



Clinical trial results:

A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when Administrated in Healthy Subjects aged 6 Months through 47 Months

Summary

EudraCT number	2018-001857-29
Trial protocol	BG EE CZ LV PL Outside EU/EEA RO
Global end of trial date	05 March 2024

Results information

Result version number	v1 (current)
This version publication date	31 August 2024
First version publication date	31 August 2024

Trial information

Trial identification

Sponsor protocol code	V130_14
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03932682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seqirus UK Limited
Sponsor organisation address	Point, 29 Market Street, Maidenhead, United Kingdom,
Public contact	Clinical Trial Disclosures, Seqirus UK Limited, Seqirus.ClinicalTrials@seqirus.com
Scientific contact	Clinical Trial Disclosures, Seqirus UK Limited, Seqirus.ClinicalTrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002068-PIP16-05
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	24 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2023
Global end of trial reached?	Yes
Global end of trial date	05 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

EFFICACY: To demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza vaccine to prevent at least one of the following:

- RT-PCR confirmed illness caused by any influenza Type A and/or Type B virus, regardless of antigenic match.
- Culture confirmed illness caused by influenza virus strains antigenically matched to the influenza strains selected for the seasonal influenza vaccine.

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations including European Directive 2001/20/EC, United States Code of Federal Regulations Title 21, ICH E6(R2), 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 May 2019
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	Bangladesh: 200
Country: Number of subjects enrolled	Bulgaria: 266
Country: Number of subjects enrolled	Czechia: 79
Country: Number of subjects enrolled	Estonia: 1246
Country: Number of subjects enrolled	Honduras: 298
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Malaysia: 65
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Pakistan: 561
Country: Number of subjects enrolled	Philippines: 1217
Country: Number of subjects enrolled	Poland: 437
Country: Number of subjects enrolled	Romania: 71
Country: Number of subjects enrolled	South Africa: 756
Country: Number of subjects enrolled	Thailand: 141
Country: Number of subjects enrolled	Ukraine: 367

Worldwide total number of subjects	5723
EEA total number of subjects	2104

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)	2532
Children (2-11 years)	3191
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 75 centers in Bangladesh (1), Bulgaria (7), Czech Republic (5), Estonia (7), Honduras (3), Latvia (1), Malaysia (5), New Zealand (2), Pakistan (5), Philippines (12), Poland (8), Romania (4), South Africa (9), Thailand (3), Ukraine (3).

Pre-assignment

Screening details:

All enrolled subjects were randomized in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QIVc

Arm description:

Cell-based quadrivalent influenza vaccine containing 2 influenza type A strains and 2 influenza type B strains

Arm type	Experimental
Investigational medicinal product name	Cell-based quadrivalent subunit influenza virus vaccine
Investigational medicinal product code	
Other name	Flucelvax Tetra
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Previously vaccinated subjects received one 0.5 mL dose administered intramuscularly on Day 1

Not previously vaccinated subjects received two 0.5 mL doses administered intramuscularly, one dose on Day 1 and one dose on Day 29

Previously vaccinated subjects were defined as subjects with a known history of at least 2 doses of an influenza vaccine prior to the current influenza season. Not previously vaccinated subjects were defined as subjects who have not received 2 or more doses of influenza vaccine prior to the current influenza season or subjects with unknown influenza vaccination history.

Arm title	Comparator
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Arm description:

Non-influenza vaccine comparator

Arm type	Non-influenza vaccine comparator
Investigational medicinal product name	Meningococcal Group C Polysaccharide Conjugate Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Previously vaccinated subjects received one 0.5 mL dose administered intramuscularly on Day 1

Not previously vaccinated subjects received one 0.5 mL dose administered intramuscularly on Day 1 and one dose of normal saline placebo on Day 29

Previously vaccinated subjects were defined as subjects with a known history of at least 2 doses of an influenza vaccine prior to the current influenza season. Not previously vaccinated subjects were defined

as subjects who have not received 2 or more doses of influenza vaccine prior to the current influenza season or subjects with unknown influenza vaccination history.

Number of subjects in period 1	QIVc	Comparator
Started	2860	2863
Completed	2794	2766
Not completed	66	97
Adverse event, serious fatal	1	2
Consent withdrawn by subject	37	45
Other	9	23
Lost to follow-up	19	25
Protocol deviation	-	2

Baseline characteristics

Reporting groups

Reporting group title	QIVc
Reporting group description: Cell-based quadrivalent influenza vaccine containing 2 influenza type A strains and 2 influenza type B strains	
Reporting group title	Comparator
Reporting group description: Non-influenza vaccine comparator	

Reporting group values	QIVc	Comparator	Total
Number of subjects	2860	2863	5723
Age categorical Units: Subjects			
6 months through 23 months	1268	1264	2532
24 months through 47 months	1592	1599	3191
Age continuous Units: months			
arithmetic mean	25.8	25.9	
standard deviation	± 11.9	± 11.9	-
Gender categorical Units: Subjects			
Female	1418	1333	2751
Male	1442	1530	2972
Race Units: Subjects			
Asian	1098	1096	2194
Black or African American	348	349	697
Native Hawaiian or Other Pacific Islander	0	1	1
White	1239	1234	2473
Other	175	183	358
Ethnic Origin Units: Subjects			
Hispanic or Latino	155	157	312
Not Hispanic or Latino	2696	2697	5393
Not reported	2	4	6
Unknown	7	5	12
Previous influenza vaccination Units: Subjects			
Previously vaccinated	48	62	110
Not previously vaccinated	2812	2801	5613
Season Units: Subjects			
Season 1	344	349	693
Season 2	497	489	986
Season 3	525	521	1046
Season 4	496	504	1000

Season 5	998	1000	1998
Country			
Units: Subjects			
Bangladesh	101	99	200
Bulgaria	131	135	266
Czechia	41	38	79
Estonia	625	621	1246
Honduras	147	151	298
Latvia	3	2	5
Malaysia	31	34	65
New Zealand	7	7	14
Pakistan	279	282	561
Philippines	608	609	1217
Poland	217	220	437
Romania	38	33	71
South Africa	376	380	756
Thailand	72	69	141
Ukraine	184	183	367
Body mass index			
Units: kg/m ²			
arithmetic mean	16.51	16.61	
standard deviation	± 2.2	± 2.9	-

End points

End points reporting groups

Reporting group title	QIVc
Reporting group description: Cell-based quadrivalent influenza vaccine containing 2 influenza type A strains and 2 influenza type B strains	
Reporting group title	Comparator
Reporting group description: Non-influenza vaccine comparator	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Full analysis
Subject analysis set description: The All Enrolled Set is all screened subjects who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a Subject ID.	
Subject analysis set title	All Exposed Set
Subject analysis set type	Full analysis
Subject analysis set description: The All Exposed Set is all subjects in the All Enrolled Set who received a study vaccination.	
Subject analysis set title	FAS Efficacy
Subject analysis set type	Full analysis
Subject analysis set description: The FAS Efficacy is all subjects in the All Enrolled Set who were randomized, received at least one dose of study vaccination, and were evaluated for efficacy at more than 14 days after the last vaccination.	
Subject analysis set title	FAS Immunogenicity
Subject analysis set type	Full analysis
Subject analysis set description: The FAS Immunogenicity is all subjects in the All Enrolled Set who were randomized, received at least one study vaccination, and provided evaluable serum samples at both baseline (Day 1) and 28 days after last vaccination (Day 29/57).	
Subject analysis set title	Solicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data indicating the occurrence or lack of occurrence of solicited AEs, ie, a subject does not have to have any solicited AEs to be included in this population.	
Subject analysis set title	Unsolicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Unsolicited Safety Set is all subjects in the All Exposed Set with unsolicited AE data.	
Subject analysis set title	Overall Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Overall Safety Set is all subjects in the Solicited Safety Set and/or Unsolicited Safety Set.	
Subject analysis set title	QIVc (Season 1)
Subject analysis set type	Full analysis
Subject analysis set description: QIVc immunogenicity analyses (Season 1)	
Subject analysis set title	Comparator (Season 1)
Subject analysis set type	Full analysis
Subject analysis set description: Comparator vaccine immunogenicity analyses (Season 1)	

Subject analysis set title	QIVc (Season 2)
Subject analysis set type	Full analysis
Subject analysis set description: QIVc immunogenicity analyses (Season 2)	
Subject analysis set title	Comparator (Season 2)
Subject analysis set type	Full analysis
Subject analysis set description: Comparator vaccine immunogenicity analyses (Season 2)	
Subject analysis set title	QIVc (Season 3)
Subject analysis set type	Full analysis
Subject analysis set description: QIVc immunogenicity analyses (Season 3)	
Subject analysis set title	Comparator (Season 3)
Subject analysis set type	Full analysis
Subject analysis set description: Comparator vaccine immunogenicity analyses (Season 3)	
Subject analysis set title	QIVc (Season 4)
Subject analysis set type	Full analysis
Subject analysis set description: QIVc immunogenicity analyses (Season 4)	
Subject analysis set title	Comparator (Season 4)
Subject analysis set type	Full analysis
Subject analysis set description: Comparator vaccine immunogenicity analyses (Season 4)	
Subject analysis set title	QIVc (Season 5)
Subject analysis set type	Full analysis
Subject analysis set description: QIVc immunogenicity analyses (Season 5)	
Subject analysis set title	Comparator (Season 5)
Subject analysis set type	Full analysis
Subject analysis set description: Comparator vaccine immunogenicity analyses (Season 5)	

Primary: Efficacy Endpoint: First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine

End point title	Efficacy Endpoint: First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine
End point description: First occurrence of reverse transcription-polymerase chain reaction (RT-PCR) confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined influenza-like illness (ILI) symptoms	
End point type	Primary
End point timeframe: >14 days after the last vaccination and until the end of the influenza season	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2835		
Units: Cases				
number (not applicable)				
RT-PCR Confirmed Influenza (Any Strain)	104	173		

Statistical analyses

Statistical analysis title	aVE, RT-PCR Confirmed Influenza, Any Strain
Statistical analysis description:	
Adjusted absolute vaccine efficacy (aVE) for QIVc versus comparator vaccine, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for previous vaccination status, sex, country, and season as random effects	
Analysis population: FAS Efficacy	
Comparison groups	QIVc v Comparator
Number of subjects included in analysis	5691
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Cox proportional hazard
Point estimate	41.26
Confidence interval	
level	Other: 97.98 %
sides	2-sided
lower limit	21.55
upper limit	56.02

Notes:

[1] - The primary objective would be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the interim analysis-adjusted lower limit of the two-sided confidence interval (CI) for aVE of QIVc versus the comparator vaccine was greater than 0%.

Primary: Efficacy Endpoint: First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine

End point title	Efficacy Endpoint: First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine
End point description:	
First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms	
End point type	Primary
End point timeframe:	
>14 days after the last vaccination and until the end of the influenza season	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2835		
Units: Cases				
number (not applicable)				
Culture Confirmed Influenza (Matched Strain)	44	82		

Statistical analyses

Statistical analysis title	aVE, Culture Confirmed Influenza, Matched Strain
Statistical analysis description:	
Adjusted aVE for QIVc versus comparator vaccine, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of culture confirmed influenza antigenically matched to the vaccine strain with vaccine group as the main effect, adjusting for previous vaccination status, sex, country, and season as random effects	
Analysis population: FAS Efficacy	
Comparison groups	QIVc v Comparator
Number of subjects included in analysis	5691
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Cox proportional hazard
Point estimate	46.9
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	19.19
upper limit	65.11

Notes:

[2] - The primary objective would be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the interim analysis-adjusted lower limit of the two-sided CI for aVE of QIVc versus the comparator vaccine was greater than 0%.

Secondary: Efficacy Endpoint: First occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine

End point title	Efficacy Endpoint: First occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine
End point description:	
First occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms	
End point type	Secondary
End point timeframe:	
>14 days after the last vaccination and until the end of the influenza season	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2835		
Units: Cases				
number (not applicable)				
Culture Confirmed Influenza (Unmatched Strain)	20	43		

Statistical analyses

Statistical analysis title	aVE, Culture Confirmed Influenza, Unmatched Strain
Statistical analysis description:	
Adjusted aVE, estimated from a Cox proportional hazard model with vaccine group as the main effect, adjusting for age group, previous vaccination status, country, and season as random effects	
Analysis population: FAS Efficacy	
Comparison groups	QIVc v Comparator
Number of subjects included in analysis	5691
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	Cox proportional hazard
Point estimate	54.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.55
upper limit	73.26

Notes:

[3] - The secondary efficacy objectives were not associated with any hypothesis testing

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

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

First occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms

End point type	Secondary
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End point timeframe:

>14 days after the last vaccination and until the end of the influenza season

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2835		
Units: Cases				
number (not applicable)				
Culture Confirmed Influenza (Any Strain)	61	121		

Statistical analyses

Statistical analysis title	aVE, Culture Confirmed Influenza, Any Strain
Statistical analysis description:	
Adjusted aVE, estimated from a Cox proportional hazard model with vaccine group as the main effect, adjusting for age group, previous vaccination status, country, and season as random effects	
Analysis population: FAS Efficacy	
Comparison groups	QIVc v Comparator
Number of subjects included in analysis	5691
Analysis specification	Pre-specified
Analysis type	other ^[4]
Parameter estimate	Cox proportional hazard
Point estimate	50.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.83
upper limit	63.77

Notes:

[4] - The secondary efficacy objectives were not associated with any hypothesis testing

Secondary: Efficacy Endpoint: First occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine

End point title	Efficacy Endpoint: First occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine
End point description:	
First occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season	
Moderate-to-severe influenza is an influenza episode complicated by one of the following diagnoses within 30 days after the ILI onset: physician confirmed lower respiratory tract illness, physician confirmed acute otitis media, or hospitalization in the ICU, physician-diagnosed serious extra-pulmonary complication of influenza or supplemental oxygen requirement for more than 8 hours	
End point type	Secondary
End point timeframe:	
>14 days after the last vaccination and until the end of the influenza season	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2835		
Units: Cases				
number (not applicable)				
Moderate-to-Severe RT-PCR Confirmed Influenza	0	9		

Statistical analyses

Statistical analysis title	aVE, Moderate-to-Severe RT-PCR Confirmed Influenza
Statistical analysis description:	
Adjusted aVE, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of Moderate-Severe RT-PCR confirmed influenza (any strain) with vaccine group as the main effect, adjusting for, previous vaccination status, sex, country and season as random effects Analysis population: FAS Efficacy	
Comparison groups	QIVc v Comparator
Number of subjects included in analysis	5691
Analysis specification	Pre-specified
Analysis type	other ^[5]
Parameter estimate	Cox proportional hazard
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99999
upper limit	100

Notes:

[5] - The secondary efficacy objectives were not associated with any hypothesis testing

Note: The lower limit of "-99999" signifies "not estimable". (The system does not allow text to be entered in the table.)

Secondary: Immunogenicity Endpoint: Pre- and postvaccination geometric mean titers (GMTs) (HI Assay)

End point title	Immunogenicity Endpoint: Pre- and postvaccination geometric mean titers (GMTs) (HI Assay)
End point description:	
HI = hemagglutination inhibition Adjusted GMTs are presented Analysis population: FAS Immunogenicity Note: For the A/H3N2 strain in Seasons 1 and 3, "99999" signifies "not applicable" due to lack of agglutination of A/H3N2 in HI assay. (The system does not allow text to be entered in the table.)	
End point type	Secondary
End point timeframe:	
Day 1 and 28 days after last vaccination	

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Geometric mean titer				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 HI GMT	40.06 (21.41 to 74.97)	44.28 (24.19 to 81.07)	22.99 (9.52 to 55.49)	27.50 (11.60 to 65.18)
A/H1N1 Day 29/57 HI GMT	126.39 (68.37 to 233.66)	60.33 (33.32 to 109.21)	60.77 (33.77 to 109.38)	11.24 (6.32 to 20.02)
A/H3N2 Day 1 HI GMT	99999 (99999 to 99999)	99999 (99999 to 99999)	12.21 (5.59 to 26.70)	14.14 (6.57 to 30.41)
A/H3N2 Day 29/57 HI GMT	99999 (99999 to 99999)	99999 (99999 to 99999)	95.36 (43.91 to 207.07)	8.79 (4.11 to 18.77)
B/Yamagata Day 1 HI GMT	11.66 (8.26 to 16.46)	11.53 (8.27 to 16.09)	9.87 (6.86 to 14.22)	8.22 (5.75 to 11.75)
B/Yamagata Day 29/57 HI GMT	18.94 (13.07 to 27.46)	6.90 (4.82 to 9.87)	23.65 (14.04 to 39.85)	13.57 (8.17 to 22.53)
B/Victoria Day 1 HI GMT	7.40 (5.35 to 10.24)	8.36 (6.11 to 11.43)	9.37 (7.46 to 11.76)	9.31 (7.45 to 11.63)
B/Victoria Day 29/57 HI GMT	14.97 (10.42 to 21.49)	7.01 (4.94 to 9.95)	16.84 (11.32 to 25.07)	8.82 (5.97 to 13.02)

End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85
Units: Geometric mean titer				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 HI GMT	10.15 (4.45 to 23.13)	8.72 (3.87 to 19.60)	57.83 (34.41 to 97.19)	58.00 (34.81 to 96.64)
A/H1N1 Day 29/57 HI GMT	49.38 (22.92 to 106.39)	5.45 (2.56 to 11.58)	149.01 (96.96 to 229.01)	81.71 (53.55 to 124.68)
A/H3N2 Day 1 HI GMT	99999 (99999 to 99999)	99999 (99999 to 99999)	46.38 (21.09 to 101.98)	35.62 (16.41 to 77.30)
A/H3N2 Day 29/57 HI GMT	99999 (99999 to 99999)	99999 (99999 to 99999)	67.88 (36.64 to 125.77)	38.85 (21.22 to 71.10)
B/Yamagata Day 1 HI GMT	7.65 (4.25 to 13.79)	7.54 (4.19 to 13.57)	8.96 (6.78 to 11.84)	9.49 (7.22 to 12.48)
B/Yamagata Day 29/57 HI GMT	13.85 (6.91 to 27.77)	5.26 (2.63 to 10.53)	13.80 (8.95 to 21.28)	4.70 (3.06 to 7.22)
B/Victoria Day 1 HI GMT	8.34 (5.40 to 12.90)	9.39 (6.12 to 14.42)	5.82 (5.18 to 6.53)	6.08 (5.42 to 6.82)
B/Victoria Day 29/57 HI GMT	9.54 (5.60 to 16.25)	4.88 (2.89 to 8.26)	23.92 (13.98 to 40.92)	4.67 (2.73 to 7.97)

End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Geometric mean titer				

geometric mean (confidence interval 95%)				
A/H1N1 Day 1 HI GMT	13.60 (1.97 to 93.97)	13.94 (1.95 to 99.61)		
A/H1N1 Day 29/57 HI GMT	362.71 (74.42 to 1767.89)	60.84 (12.14 to 304.84)		
A/H3N2 Day 1 HI GMT	82.67 (19.98 to 342.16)	120.80 (28.47 to 512.58)		
A/H3N2 Day 29/57 HI GMT	440.30 (127.04 to 1526.08)	57.87 (16.29 to 205.63)		
B/Yamagata Day 1 HI GMT	7.30 (4.19 to 12.73)	7.35 (4.18 to 12.95)		
B/Yamagata Day 29/57 HI GMT	53.72 (20.85 to 138.40)	8.04 (3.07 to 21.06)		
B/Victoria Day 1 HI GMT	7.84 (1.38 to 44.61)	5.92 (1.01 to 34.73)		
B/Victoria Day 29/57 HI GMT	539.53 (158.62 to 1835.19)	45.34 (13.01 to 157.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Seroconversion rate (SCR) (HI Assay)

End point title	Immunogenicity Endpoint: Seroconversion rate (SCR) (HI Assay)
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End point description:

The SCR is defined as the percentage of subjects with 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

Analysis population: FAS Immunogenicity

Note: For the A/H3N2 strain in Seasons 1 and 3, "99999" signifies "not applicable" due to lack of agglutination of A/H3N2 in HI assay".

For the B/Victoria strain in the Comparator group in Season 3, the 95% CI values of "-99999 to 99999" signify "not estimable". (The system does not allow text to be entered in the table.)

End point type	Secondary
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End point timeframe:

Day 1 and 28 days after last vaccination

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR HI Titer	45.54 (36.10 to 55.22)	12.04 (6.57 to 19.70)	57.01 (47.08 to 66.54)	3.60 (0.99 to 8.97)
A/H3N2 SCR HI Titer	99999 (99999 to 99999)	99999 (99999 to 99999)	70.09 (60.48 to 78.56)	6.31 (2.57 to 12.56)
B/Yamagata SCR HI Titer	37.50 (28.53 to 47.15)	3.70 (1.02 to 9.21)	24.30 (16.53 to 33.54)	6.31 (2.57 to 12.56)

B/Victoria SCR HI Titer	24.11 (16.53 to 33.10)	2.78 (0.58 to 7.90)	13.08 (7.34 to 20.98)	0.90 (0.02 to 4.92)
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End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR HI Titer	68.47 (58.96 to 76.96)	2.68 (0.56 to 7.63)	29.89 (20.54 to 40.65)	4.71 (1.30 to 11.61)
A/H3N2 SCR HI Titer	99999 (99999 to 99999)	99999 (99999 to 99999)	44.83 (34.15 to 55.87)	28.24 (19.00 to 39.04)
B/Yamagata SCR HI Titer	23.42 (15.91 to 32.41)	0.90 (0.02 to 4.92)	29.89 (20.54 to 40.65)	1.18 (0.03 to 6.38)
B/Victoria SCR HI Titer	9.91 (5.05 to 17.04)	0 (-99999 to 99999)	42.53 (31.99 to 53.59)	3.53 (0.73 to 9.97)

End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR HI Titer	75.00 (65.75 to 82.83)	12.96 (7.27 to 20.79)		
A/H3N2 SCR HI Titer	84.26 (76.00 to 90.55)	15.74 (9.45 to 24.00)		
B/Yamagata SCR HI Titer	66.67 (56.95 to 75.45)	3.70 (1.02 to 9.21)		
B/Victoria SCR HI Titer	80.56 (71.83 to 87.54)	8.33 (3.88 to 15.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Geometric mean ratio (GMR) (HI Assay)

End point title	Immunogenicity Endpoint: Geometric mean ratio (GMR) (HI Assay)
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End point description:

The GMR is defined as the geometric mean of the fold increase of postvaccination HI titer over the prevaccination HI titer. Adjusted GMRs are presented.

Analysis population: FAS Immunogenicity

Note: For the A/H3N2 strain in Seasons 1 and 3, "99999" signifies "not applicable" due to lack of agglutination of A/H3N2 in HI assay".

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End point type	Secondary
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End point timeframe:

Day 1 and 28 days after last vaccination

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR HI Titer	3.36 (1.69 to 6.66)	1.53 (0.79 to 2.95)	3.71 (2.04 to 6.73)	0.67 (0.37 to 1.20)
A/H3N2 GMR HI Titer	99999 (99999 to 99999)	99999 (99999 to 99999)	7.43 (2.95 to 18.75)	0.62 (0.25 to 1.54)
B/Yamagata GMR HI Titer	2.52 (1.75 to 3.63)	0.92 (0.65 to 1.31)	3.38 (2.02 to 5.67)	1.96 (1.18 to 3.25)
B/Victoria GMR HI Titer	2.01 (1.37 to 2.96)	0.90 (0.62 to 1.30)	1.79 (1.15 to 2.79)	0.94 (0.61 to 1.46)

End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR HI Titer	6.28 (2.91 to 13.56)	0.70 (0.33 to 1.50)	2.59 (1.51 to 4.45)	1.42 (0.83 to 2.41)
A/H3N2 GMR HI Titer	99999 (99999 to 99999)	99999 (99999 to 99999)	1.81 (0.86 to 3.81)	1.19 (0.57 to 2.48)
B/Yamagata GMR HI Titer	1.95 (0.91 to 4.15)	0.75 (0.35 to 1.59)	2.03 (1.32 to 3.13)	0.68 (0.44 to 1.04)
B/Victoria GMR HI Titer	1.43 (0.83 to 2.44)	0.71 (0.42 to 1.21)	4.44 (2.62 to 7.55)	0.85 (0.51 to 1.43)

End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR HI Titer	19.20 (3.61 to 102.12)	3.20 (0.58 to 17.52)		
A/H3N2 GMR HI Titer	7.14 (1.81 to 28.16)	0.80 (0.20 to 3.24)		
B/Yamagata GMR HI Titer	8.04 (3.12 to 20.72)	1.20 (0.46 to 3.15)		
B/Victoria GMR HI Titer	32.55 (8.85 to 119.71)	2.95 (0.78 to 11.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: Pre- and postvaccination GMTs (MN Assay)

End point title	Immunogenicity Endpoint: Pre- and postvaccination GMTs (MN Assay)
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End point description:

MN = microneutralization

Adjusted GMTs are presented

Analysis population: FAS Immunogenicity

End point type	Secondary
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End point timeframe:

Day 1 and 28 days after last vaccination

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Geometric mean titer				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 MN GMT	22.06 (9.53 to 51.07)	31.10 (13.83 to 69.92)	57.54 (18.79 to 176.16)	55.89 (18.69 to 167.19)
A/H1N1 Day 29/57 MN GMT	329.08 (196.16 to 552.06)	36.24 (21.97 to 59.79)	473.15 (247.69 to 903.85)	66.69 (35.39 to 125.71)
A/H3N2 Day 1 MN GMT	6.92 (4.91 to 9.76)	6.29 (4.51 to 8.76)	4.96 (4.19 to 5.88)	4.80 (4.07 to 5.67)
A/H3N2 Day 29/57 MN GMT	27.55 (18.70 to 40.58)	10.95 (7.52 to 15.94)	12.04 (7.60 to 19.08)	5.31 (3.38 to 8.34)
B/Yamagata Day 1 MN GMT	76.91 (53.50 to 110.55)	66.14 (46.60 to 93.87)	65.25 (35.87 to 118.70)	60.03 (33.41 to 107.86)
B/Yamagata Day 29/57 MN GMT	278.89 (202.31 to 384.46)	88.67 (65.06 to 120.84)	283.42 (183.07 to 438.79)	126.59 (82.43 to 194.41)
B/Victoria Day 1 MN GMT	6.07 (4.82 to 7.65)	6.64 (5.31 to 8.30)	4.99 (4.16 to 5.99)	5.18 (4.33 to 6.18)
B/Victoria Day 29/57 MN GMT	14.23 (10.95 to 18.51)	7.00 (5.44 to 9.02)	5.29 (4.03 to 6.92)	5.26 (4.04 to 6.85)

End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85

Units: Geometric mean titer				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 MN GMT	61.40 (16.51 to 228.37)	43.43 (11.93 to 158.11)	32.15 (19.17 to 53.90)	35.32 (21.25 to 58.71)
A/H1N1 Day 29/57 MN GMT	459.87 (157.55 to 1342.31)	19.32 (6.76 to 55.21)	86.91 (58.51 to 129.11)	46.51 (31.53 to 68.60)
A/H3N2 Day 1 MN GMT	7.02 (3.18 to 15.51)	8.33 (3.82 to 18.16)	17.70 (10.34 to 30.31)	15.77 (9.29 to 26.76)
A/H3N2 Day 29/57 MN GMT	57.93 (28.43 to 118.06)	10.49 (5.21 to 21.09)	35.99 (18.52 to 69.94)	14.78 (7.70 to 28.34)
B/Yamagata Day 1 MN GMT	15.33 (7.73 to 30.41)	15.26 (7.78 to 29.93)	53.41 (32.42 to 88.00)	54.11 (33.12 to 88.41)
B/Yamagata Day 29/57 MN GMT	55.17 (27.19 to 111.92)	19.24 (9.59 to 38.59)	84.60 (55.74 to 128.38)	52.11 (34.57 to 78.55)
B/Victoria Day 1 MN GMT	9.09 (4.80 to 17.24)	10.71 (5.71 to 20.09)	8.79 (6.40 to 12.07)	7.72 (5.66 to 10.55)
B/Victoria Day 29/57 MN GMT	26.81 (14.06 to 51.12)	9.65 (5.12 to 18.20)	121.02 (59.56 to 245.87)	5.99 (2.99 to 11.97)

End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Geometric mean titer				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 MN GMT	113.94 (36.64 to 354.34)	115.49 (36.41 to 366.35)		
A/H1N1 Day 29/57 MN GMT	352.09 (110.01 to 1126.90)	86.61 (26.51 to 282.92)		
A/H3N2 Day 1 MN GMT	26.08 (7.79 to 87.37)	25.98 (7.59 to 88.87)		
A/H3N2 Day 29/57 MN GMT	139.97 (41.52 to 471.84)	30.22 (8.78 to 104.08)		
B/Yamagata Day 1 MN GMT	51.81 (23.27 to 115.35)	45.20 (20.02 to 102.06)		
B/Yamagata Day 29/57 MN GMT	169.24 (75.01 to 381.86)	49.34 (21.58 to 112.85)		
B/Victoria Day 1 MN GMT	15.97 (2.53 to 100.98)	12.20 (1.87 to 79.68)		
B/Victoria Day 29/57 MN GMT	938.65 (230.67 to 3819.51)	39.32 (9.41 to 164.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: SCR (MN Assay)

End point title	Immunogenicity Endpoint: SCR (MN Assay)
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End point description:

The SCR is defined as the percentage of subjects with either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40, or a prevaccination MN titer ≥1:10 and a ≥4-fold increase in postvaccination MN titer

Analysis population: FAS Immunogenicity

End point type	Secondary
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End point timeframe:

Day 1 and 28 days after last vaccination

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR MN Titer	73.21 (64.02 to 81.14)	2.78 (0.58 to 7.90)	74.77 (65.45 to 82.67)	4.50 (1.48 to 10.20)
A/H3N2 SCR MN Titer	38.39 (29.36 to 48.06)	4.63 (1.52 to 10.47)	20.56 (13.36 to 29.46)	1.80 (0.22 to 6.36)
B/Yamagata SCR MN Titer	46.43 (36.95 to 56.10)	0.93 (0.02 to 5.05)	30.84 (22.27 to 40.50)	3.60 (0.99 to 8.97)
B/Victoria SCR MN Titer	20.54 (13.49 to 29.20)	0.93 (0.02 to 5.05)	0.93 (0.02 to 5.10)	2.70 (0.56 to 7.70)

End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR MN Titer	87.39 (79.74 to 92.93)	4.46 (1.47 to 10.11)	32.18 (22.56 to 43.06)	7.06 (2.63 to 14.73)
A/H3N2 SCR MN Titer	57.66 (47.92 to 66.98)	1.79 (0.22 to 6.30)	33.33 (23.58 to 44.25)	10.59 (4.96 to 19.15)
B/Yamagata SCR MN Titer	36.94 (27.97 to 46.62)	4.46 (1.47 to 10.11)	19.54 (11.81 to 29.43)	4.71 (1.30 to 11.61)
B/Victoria SCR MN Titer	25.23 (17.46 to 34.35)	0.89 (0.02 to 4.87)	87.36 (78.50 to 93.52)	7.06 (2.63 to 14.73)

End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Percentage of participants				
number (confidence interval 95%)				
A/H1N1 SCR MN Titer	68.52 (58.88 to 77.12)	15.74 (9.45 to 24.00)		
A/H3N2 SCR MN Titer	71.30 (61.80 to 79.59)	15.74 (9.45 to 24.00)		

B/Yamagata SCR MN Titer	54.63 (44.76 to 64.24)	7.41 (3.25 to 14.07)		
B/Victoria SCR MN Titer	94.44 (88.30 to 97.93)	9.26 (4.53 to 16.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity Endpoint: GMR (MN Assay)

End point title	Immunogenicity Endpoint: GMR (MN Assay)
End point description:	
The GMR is defined as the geometric mean of the fold increase of postvaccination MN titer over the prevaccination MN titer. Adjusted GMRs are presented.	
Analysis population: FAS Immunogenicity	
End point type	Secondary
End point timeframe:	
Day 1 and 28 days after vaccination	

End point values	QIVc (Season 1)	Comparator (Season 1)	QIVc (Season 2)	Comparator (Season 2)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	108	107	111
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR MN Titer	16.16 (9.52 to 27.45)	1.70 (1.02 to 2.83)	8.12 (4.19 to 15.75)	1.15 (0.60 to 2.20)
A/H3N2 GMR MN Titer	3.28 (2.23 to 4.84)	1.32 (0.91 to 1.92)	2.14 (1.35 to 3.40)	0.93 (0.59 to 1.46)
B/Yamagata GMR MN Titer	3.93 (2.81 to 5.49)	1.30 (0.94 to 1.79)	3.05 (1.95 to 4.75)	1.38 (0.89 to 2.13)
B/Victoria GMR MN Titer	2.17 (1.67 to 2.82)	1.07 (0.83 to 1.37)	1.04 (0.77 to 1.40)	1.01 (0.75 to 1.35)

End point values	QIVc (Season 3)	Comparator (Season 3)	QIVc (Season 4)	Comparator (Season 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	111	112	87	85
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR MN Titer	17.55 (5.72 to 53.86)	0.81 (0.27 to 2.44)	2.37 (1.54 to 3.67)	1.23 (0.80 to 1.88)
A/H3N2 GMR MN Titer	5.92 (2.79 to 12.56)	1.01 (0.48 to 2.13)	2.74 (1.39 to 5.38)	1.16 (0.60 to 2.26)
B/Yamagata GMR MN Titer	3.15 (1.47 to 6.71)	1.10 (0.52 to 2.32)	1.82 (1.15 to 2.88)	1.11 (0.71 to 1.75)

B/Victoria GMR MN Titer	2.74 (1.37 to 5.47)	0.92 (0.47 to 1.83)	16.90 (8.36 to 34.19)	0.86 (0.43 to 1.72)
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End point values	QIVc (Season 5)	Comparator (Season 5)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	108		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
A/H1N1 GMR MN Titer	3.47 (1.07 to 11.24)	0.85 (0.26 to 2.81)		
A/H3N2 GMR MN Titer	4.40 (1.30 to 14.88)	0.95 (0.27 to 3.28)		
B/Yamagata GMR MN Titer	3.81 (1.56 to 9.33)	1.19 (0.48 to 2.95)		
B/Victoria GMR MN Titer	31.51 (7.19 to 138.05)	1.42 (0.31 to 6.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Percentage of subjects with solicited local and systemic adverse events (AEs) was assessed for 7 days following each vaccination in the QIVc group and the comparator group

End point title	Safety Endpoint: Percentage of subjects with solicited local and systemic adverse events (AEs) was assessed for 7 days following each vaccination in the QIVc group and the comparator group
End point description:	
Analysis population: Solicited Safety Set	
End point type	Secondary
End point timeframe:	
7 days following each vaccination	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2813	2790		
Units: Percentage of subjects				
number (not applicable)				
Solicited AEs	55.8	60.8		
Solicited Local AEs	32.3	40.4		
Solicited Systemic AEs	40.9	42.5		
Analgesic/Antipyretic Use	14.5	15.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Percentage of subjects with any unsolicited AEs was assessed in the QIVc group and in the comparator group until 28 days after each vaccination

End point title	Safety Endpoint: Percentage of subjects with any unsolicited AEs was assessed in the QIVc group and in the comparator group until 28 days after each vaccination
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End point description:

Analysis population: Unsolicited Safety Set

End point type	Secondary
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End point timeframe:

28 days following each vaccination

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2841		
Units: Percentage of participants				
number (not applicable)				
Any AE	42.5	45.4		
Any related AE	4.2	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Percentage of subjects with serious adverse events (SAEs), new onset of chronic disease (NOCD), AEs leading to withdrawal from the study or vaccination

End point title	Safety Endpoint: Percentage of subjects with serious adverse events (SAEs), new onset of chronic disease (NOCD), AEs leading to withdrawal from the study or vaccination
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End point description:

Analysis population: Unsolicited Safety Set

End point type	Secondary
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End point timeframe:

Day 1 through Study Completion

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2841		
Units: Percentage of subjects				
number (not applicable)				
SAE	2.2	3.0		
Related SAE	0	0.04		
NOCD	0.7	0.4		
AE leading to study withdrawal	0	0		
AE leading to study vaccine withdrawal	0	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Endpoint: Percentage of subjects with medically-attended AEs within 30 days after influenza-like illness (ILI) onset

End point title	Safety Endpoint: Percentage of subjects with medically-attended AEs within 30 days after influenza-like illness (ILI) onset
End point description:	
Analysis population: Unsolicited Safety Set	
End point type	Secondary
End point timeframe:	
30 days following ILI onset	

End point values	QIVc	Comparator		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2856	2841		
Units: Percentage of participants				
number (not applicable)				
Medically-attended AE within 30 days of ILI onset	28.9	32.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through Study Completion

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	QIVc
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Reporting group description:

Cell-based quadrivalent influenza vaccine containing 2 influenza type A strains and 2 influenza type B strains

Reporting group title	Comparator
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Reporting group description:

Non-influenza vaccine comparator

Serious adverse events	QIVc	Comparator	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 2856 (2.24%)	84 / 2841 (2.96%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	2 / 2856 (0.07%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Accidental exposure to product			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 2856 (0.00%)	2 / 2841 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	1 / 2856 (0.04%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular dysfunction			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (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			
Febrile convulsion			

subjects affected / exposed	5 / 2856 (0.18%)	3 / 2841 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intussusception			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 2856 (0.04%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (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			
Asthma			
subjects affected / exposed	2 / 2856 (0.07%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Wheezing			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hypertransaminaemia			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (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			
Pneumonia			
subjects affected / exposed	15 / 2856 (0.53%)	24 / 2841 (0.84%)	
occurrences causally related to treatment / all	0 / 15	1 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	8 / 2856 (0.28%)	12 / 2841 (0.42%)	
occurrences causally related to treatment / all	0 / 8	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dengue fever			
subjects affected / exposed	6 / 2856 (0.21%)	7 / 2841 (0.25%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	4 / 2856 (0.14%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 2856 (0.11%)	6 / 2841 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	2 / 2856 (0.07%)	3 / 2841 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Otitis media acute			
subjects affected / exposed	2 / 2856 (0.07%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	2 / 2856 (0.07%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	2 / 2856 (0.07%)	2 / 2841 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 2856 (0.07%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	2 / 2856 (0.07%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (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 / 2856 (0.04%)	3 / 2841 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			

subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 2856 (0.04%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 2856 (0.04%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus infection			
subjects affected / exposed	1 / 2856 (0.04%)	2 / 2841 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (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 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 2856 (0.04%)	2 / 2841 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	0 / 2856 (0.00%)	2 / 2841 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebiasis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
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 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human herpesvirus 6 infection			

subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (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 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
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	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 2856 (0.00%)	3 / 2841 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 2856 (0.07%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 2856 (0.04%)	0 / 2841 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 2856 (0.00%)	1 / 2841 (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	Comparator	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1121 / 2856 (39.25%)	1176 / 2841 (41.39%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	576 / 2856 (20.17%)	634 / 2841 (22.32%)	
occurrences (all)	852	933	

Rhinitis			
subjects affected / exposed	282 / 2856 (9.87%)	290 / 2841 (10.21%)	
occurrences (all)	324	319	
Nasopharyngitis			
subjects affected / exposed	255 / 2856 (8.93%)	255 / 2841 (8.98%)	
occurrences (all)	371	397	
Respiratory tract infection			
subjects affected / exposed	162 / 2856 (5.67%)	158 / 2841 (5.56%)	
occurrences (all)	190	185	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2018	Version 1.0 to Version 2.0 The main reasons for the protocol amendment were: 1. Omission of the option of placebo only as the comparator vaccine; all subjects in the comparator group were to receive <i>Neisseria meningitidis</i> serogroup C polysaccharide conjugate vaccine. 2. Modification of an exclusion criterion to exclude subjects with prior documented <i>Neisseria meningitidis</i> serogroup C disease from the study. 3. Reduction in the volume of blood drawn per time point from a maximum of 7 mL per blood draw to a maximum of 5 mL per blood draw. 4. Revision of the description of the route of temperature measurement to indicate that there was not a preferred route of measurement.
03 September 2020	Version 2.0 to Version 3.0 The main reasons for the protocol amendment were: 1. Removal of constraints on a minimum number of subjects to be recruited or a minimum number of influenza seasons in which the study would be conducted. 2. Addition of exploratory objectives to characterize immune response by other assays and use genotypic methods to characterize strains of circulating influenza virus from NP swabs collected during the study. 3. Inclusion of other study assessments, in addition to collection of a NP swab specimen, at home visits when deemed necessary and agreed to by the Sponsor, eg, during the COVID-19 pandemic situation. 4. Permitting Remote Source Data Verification when deemed necessary, eg, during the COVID-19 pandemic situation. 5. Modification of the description of the residual amount of MDCK cell protein and protein other than HA in alignment with the Package Insert/SmPC for Flucelvax Quadrivalent/Flucelvax Tetra. 6. Harmonization of the text in Section 8.6 Interim Analysis of the protocol to state that the DMC may recommend to stop the study for efficacy when at least one efficacy objective met the success criteria, and adjusting the CI and overall alpha for hypothesis testing for the primary objectives during the interim analysis to meet the overall coverage of 97.5% CI and alpha being 1.25% (one sided), respectively.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	The Northern Hemisphere (NH) 2019/2020 study season was shortened in duration due to the onset of the COVID-19 pandemic in March 2020 and conduct of the study was cancelled for the Southern Hemisphere (SH) 2020 season. The study was restarted for the NH 2020/2021 influenza season.	11 September 2020
02 September 2021	The NH 2020/2021 season was conducted; however, the SH 2021 and NH 2021/2022 study seasons were cancelled due to the significant reduction in global influenza activity observed with the pandemic. The study was restarted for the NH 2022/2023 influenza season.	14 September 2022

Notes:

Limitations and caveats

None reported