Clinical trial results:
A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months

Summary

EudraCT number	2020-002785-13
Trial protocol	Outside EU/EEA
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021

Trial information

Trial identification

Sponsor protocol code	V130_10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04074928
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SEQIRUS
Sponsor organisation address	475 Green Oaks Parkway, Holly Springs, North Carolina, United States, 27540
Public contact	l Disclosure Manager, Seqirus, Inc., Clinical Trial, Seqirus.Clinicaltrials@seqirus.com
Scientific contact	Disclosure Manager, Seqirus, Inc., Clinical Trial , Seqirus.Clinicaltrials@seqirus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002068-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2020
Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 - 47 months of age, as measured by hemagglutination inhibition (HAI) assay for A/H1N1, B/Yamagata and B/Victoria strains and by microneutralization (MN) assay for A/H3N2 strain, using cell-derived target viruses.

Successful demonstration of the primary immunogenicity objective meant all 8 co-primary immunogenicity endpoints were achieved. Specifically, QIVc would be considered noninferior to US-licensed QIV if, for each of the 4 strains, these statistical criteria were met:

- The upper bound of the 2-sided 95% confidence interval (CI) did not exceed the prespecified noninferiority margin of 1.5 for the Day 29/57 Geometric Mean Titre (GMT) ratio
- The upper bound of the 2-sided 95% CI did not exceed the prespecified noninferiority margin of 10% for the Day 29/57 Seroconversion Rate (SCR) difference

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki. Only subjects who met all of the eligibility criteria were enrolled and vaccinated in the study. Potential subjects with allergy to any component of the vaccine or a history of serious vaccine reactions were not included in the study. Vaccinations were performed by trained, qualified healthcare professionals. After vaccination, subjects remained under medical supervision and were monitored for any immediate postvaccination reactions for at least 30 minutes

Background therapy: -

Evidence for comparator:

Consistent with US Food and Drug Administration (FDA) Guidance on the choice of control group, a US-licensed quadrivalent vaccine against seasonal influenza was chosen as the active comparator to allow evaluation of QIVc against a quadrivalent influenza vaccine associated with protection from influenza

Actual start date of recruitment	06 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 2414
Worldwide total number of subjects	2414
EEA total number of subjects	0

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)	902
Children (2-11 years)	1512
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:

This study was conducted at 47 centers in the United States.

Pre-assignment

Screening details:

A total of 2414 subjects were enrolled in the study, of whom 2402 subjects received study vaccine.

Period 1

Period 1 title	Period 1 (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 an observer-blind study. Vaccine administration was shielded from the subject's parent(s)/Legally Acceptable Representative(s) and blinded study personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	QIVc

Arm description:

Enrolled subjects who were randomized and received QIVc
Analysis set type = FAS

Arm type	Experimental
Investigational medicinal product name	Inactivated quadrivalent influenza vaccine
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:

Previously vaccinated subjects received a 0.5 mL IM dose of QIVc on Day 1; not previously vaccinated subjected received a 0.5 mL IM dose of QIVc on Day 1 and Day 29.

Arm title	US-licensed QIV

Arm description:

Enrolled subjects who were randomized and received the US-licensed QIV
Analysis set type = FAS

Arm type	Active comparator
Investigational medicinal product name	US-licensed QIV
Investigational medicinal product code	
Other name	US licensed QIV
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Previously vaccinated subjects received an IM dose of the US-licensed QIV on Day 1; not previously vaccinated subjected received an IM dose of the US-licensed QIV on Day 1 and Day 29. The dose was 0.25 mL for subjects 6 months through 35 months of age and 0.5 mL for subjects 36 months through 47 months of age.

Number of subjects in period 1[1]	QIVc	US-licensed QIV
Started	1597	805
Completed	1362	706
Not completed	235	99
Adverse event, serious fatal	2	-
Consent withdrawn by subject	36	16
Adverse event, non-fatal	1	-
no matching reasons found	5	-
Nothing matched	-	7
Lost to follow-up	191	76

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 2414 who enrolled in the study 12 subjects were not exposed leaving 2402 subjects in the FAS.

Baseline characteristics

Reporting groups	
Reporting group title	QIVc
Reporting group description:	
Enrolled subjects who were randomized and received QIVc Analysis set type = FAS	
Reporting group title	US-licensed QIV
Reporting group description:	
Enrolled subjects who were randomized and received the US-licensed QIV Analysis set type = FAS	

Reporting group values	QIVc	US-licensed QIV	Total
Number of subjects	1597	805	2402
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)	595	299	894
Children (2-11 years)	1002	506	1508
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: months			
arithmetic mean	28.1	28.2	
standard deviation	± 11.54	± 11.63	-
Gender categorical			
Units: Subjects			
Female	794	399	1193
Male	803	406	1209

End points

End points reporting groups

Reporting group title	QIVc

Reporting group description:

Enrolled subjects who were randomized and received QIVc
Analysis set type = FAS

Reporting group title	US-licensed QIV

Reporting group description:

Enrolled subjects who were randomized and received the US-licensed QIV
Analysis set type = FAS

Subject analysis set title	GMT Ratio (US-licensed QIV/QIVc)
Subject analysis set type	Per protocol

Subject analysis set description:

US-licensed QIV: Subjects in this group received the following the dose recommendations described in the US Package Insert, ie, previously vaccinated subjects received an IM dose of 0.25 mL for subjects 6 months through 35 months of age and 0.5 mL for subjects 36 months through 47 months of age Day 1 while not previously vaccinated subjected received an IM dose on Day 1 and Day 29.

QIVc: Previously vaccinated subjects in this group received a 0.5 mL IM dose of QIVc on Day 1 while not previously vaccinated subjected received a 0.5 mL IM dose of QIVc on Day 1 and Day 29

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Primary: Primary: Co-Primary Immunogenicity: Geometric mean titre (GMT) ratios for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV

End point title	Primary: Co-Primary Immunogenicity: Geometric mean titre (GMT) ratios for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV

End point description:

The 8 co-primary immunogenicity endpoints were the GMT ratios and SCR differences for the 4 vaccine strains, using cell-derived target viruses, as measured by:

- HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains
- MN assay for the A/H3N2 strain

The GMT ratio was defined as the geometric mean of the postvaccination (28 days after last vaccination) HAI or MN titre for the US-licensed QIV divided by the geometric mean of the posstvaccination HAI or MN titre for QIVc.

End point type	Primary

End point timeframe:

End point timeframe: 28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092[1]	575[2]		
Units: GMT				
geometric mean (confidence interval 95%)				
A/H1N1	78.0 (70.75 to 86.03)	57.3 (50.76 to 64.63)		
A/H3N2	23.1 (21.21 to 25.12)	23.9 (21.57 to 26.57)		
B/YAMAGATA	35.6 (32.93 to 38.58)	26.0 (23.54 to 28.63)		
B/VICTORIA	22.4 (20.70 to 24.19)	19.6 (17.81 to 21.58)		

Notes:

[1] - N=1078 for the A/H3N2 strain

[2] - N=572 for the A/H3H2 Strain

Statistical analyses

Statistical analysis title	Noninferiority, A/H1N1, GMT ratio, Day 29/57

Statistical analysis description:

Non-inferiority of the immune response to the A/H1N1 vaccine strain measured by GMT ratio [US-licensed QIV GMT/QIVc GMT] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	GMT Ratio
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	0.836

Notes:

[3] - The non-inferiority criterion for the GMT ratio (adjusted analysis) was that the upper limit of the 2-sided 95% CI did not exceed the pre-specified non-inferiority margin of 1.5 for the Day 29/57 GMT ratio.

Statistical analysis title	0Noninferiority, A/H3N2, GMT ratio, Day 29/57

Statistical analysis description:

Non-inferiority of the immune response to the A/H3N2 vaccine strain measured by GMT ratio [US-licensed QIV GMT/QIVc GMT] 28 days after the last vaccination,

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	GMT Ratio
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.16

Notes:

[4] - The noninferiority criterion for the GMT ratio (adjusted analysis) was that the upper limit of the 2-sided 95% CI did not exceed the prespecified noninferiority margin of 1.5 for the Day 29/57 GMT ratio.

NOTE: FOR JUST THE A/H3N2 STRAIN, N= 1650

Statistical analysis title	Noninferiority, B/Yamagata, GMT ratio, Day 29/57

Statistical analysis description:

Noninferiority of the immune response to the B/Yamagata vaccine strain measured by GMT ratio [US-licensed QIV GMT/QIVc GMT] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMT Ratio
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	0.809

Notes:

[5] - The noninferiority criterion for the GMT ratio (adjusted analysis) was that the upper limit of the 2-sided 95% CI did not exceed the prespecified noninferiority margin of 1.5 for the Day 29/57 GMT ratio.

Statistical analysis title	Noninferiority, B/Victoria, GMT ratio, Day 29/57

Statistical analysis description:

Noninferiority of the immune response to the B/Victoria vaccine strain measured by GMT ratio [US-licensed QIV GMT/QIVc GMT] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMT Ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.791
upper limit	0.972

Notes:

[6] - The noninferiority criterion for the GMT ratio (adjusted analysis) was that the upper limit of the 2-sided 95% CI did not exceed the prespecified noninferiority margin of 1.5 for the Day 29/57 GMT ratio.

Primary: Primary: Co-Primary Immunogenicity: Seroconversion rate (SCR) differences for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV

End point title	Primary: Co-Primary Immunogenicity: Seroconversion rate (SCR) differences for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed

	QIV

End point description:

End point type	Primary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092	575		
Units: SCR				
number (confidence interval 95%)				
A/H1N1	58.24 (55.25 to 61.19)	46.78 (42.64 to 50.96)		
A/H3N2	27.64 (24.99 to 30.42)	30.77 (27.01 to 34.73)		
B/YAMAGATA	46.52 (43.53 to 49.53)	31.65 (27.87 to 35.63)		
B/VICTORIA	30.31 (27.60 to 33.13)	24.35 (20.89 to 28.07)		

Statistical analyses

Statistical analysis title	Noninferiority, A/H1N1, SCR difference, Day 29/57

Statistical analysis description:

Non-inferiority of the immune response to the A/H1N1 vaccine strain measured by SCR difference [SCR US-licensed QIV minus SCR QIVc] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	SCR Difference
Point estimate	-11.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.45
upper limit	-6.423

Notes:

[7] - The non-inferiority criterion for the SCR difference was that the upper limit of the 2-sided 95% CI did not exceed the pre-specified non-inferiority margin of 10% for the Day 29/57 SCR difference.

Statistical analysis title	Noninferiority, A/H3N2, SCR difference, Day 29/57

Statistical analysis description:

Non-inferiority of the immune response to the A/H3N2 vaccine strain measured by SCR difference [SCR US-licensed QIV minus SCR QIVc] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	SCR Difference
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	7.81

Notes:

[8] - The non-inferiority criterion for the SCR difference was that the upper limit of the 2-sided 95% CI did not exceed the pre-specified non-inferiority margin of 10% for the Day 29/57 SCR difference.

NOTE: FOR JUST THE A/H3N2 STRAIN, N= 1650

Statistical analysis title	Noninferiority, B/Yamagata, SCR differencev D29/57

Statistical analysis description:

Non-inferiority of the immune response to the B/Yamagata vaccine strain measured by SCR difference [SCR US-licensed QIV minus SCR QIVc] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV
Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	SCR Difference
Point estimate	-14.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.61
upper limit	-9.983

Notes:

[9] - The non-inferiority criterion for the SCR difference was that the upper limit of the 2-sided 95% CI did not exceed the pre-specified non-inferiority margin of 10% for the Day 29/57 SCR difference.

Statistical analysis title	Noninferiority, B/Victoria, CR differencev D29/57

Statistical analysis description:

Non-inferiority of the immune response to the B/Victoria vaccine strain measured by SCR difference [SCR US-licensed QIV minus SCR QIVc] 28 days after the last vaccination

Comparison groups	QIVc v US-licensed QIV

Number of subjects included in analysis	1667
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	SCR Difference
Point estimate	-5.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.33
upper limit	-1.44

Notes:

[10] - The non-inferiority criterion for the SCR difference was that the upper limit of the 2-sided 95% CI did not exceed the pre-specified non-inferiority margin of 10% for the Day 29/57 SCR difference.

Secondary: Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg-derived target viruses

End point title	Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg-derived target viruses

End point description:

Objective 1a - GMTs were assessed at Day 1 and Day 29/57 for the 4 vaccine strains, using egg-derived target viruses, as measured by:
- HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains
- MN assay for the A/H3N2 strain

Dataset used: PPS (see Primary Immunogenicity endpoints section for full definition)

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092[11]	575[12]		
Units: GMT				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 GMT	14.0 (12.54 to 15.74)	13.9 (12.11 to 16.0)		
A/H1N1 Day 29/57 GMT	92.2 (83.62 to 101.71)	82.9 (73.51 to 93.5)		
A/H3N2 Day 1 GMT	12.9 (11.87 to 13.96)	12.60 (11.42 to 13.95)		
A/H3N2 Day 29/57 GMT	43.4 (39.58 to 47.52)	44.70 (39.98 to 50.08)		
B/Yamagata Day 1 GMT	6.7 (6.33 to 7.16)	6.70 (6.23 to 7.26)		
B/Yamagata Day 29/57 GMT	23.0 (21.21 to 24.89)	24.70 (22.39 to 27.26)		

B/Victoria Day 1 GMT	6.1 (5.77 to 6.38)	6.00 (5.68 to 6.43)		
B/Victoria Day 29/57 GMT	13.6 (12.58 to 14.61)	14.80 (13.46 to 16.19)		

Notes:

[11] - N=1079 for the A/H3N2 Strain

[12] - N=572 for the A/H3N2 Strain

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMT ratio for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg-derived target viruses

End point title	Secondary Immunogenicity: GMT ratio for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg-derived target viruses

End point description:

Objective 1b - The GMT ratio is the geometric mean of the postvaccination (28 days after last vaccination) HAI or MN titre for the US-licensed QIV divided by the geometric mean of the postvaccination HAI or MN titre for QIVc. Dataset used: PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects

End point values	GMT Ratio (US-licensed QIV/QIVc)			
Subject group type	Subject analysis set			
Number of subjects analysed	1667[13]			
Units: GMT Ratio				
number (confidence interval 95%)				
A/H1N1	0.90 (0.80 to 1.02)			
A/H3N2	1.03 (0.91 to 1.16)			
B/Yamagata	1.08 (0.97 to 1.19)			
B/Victoria	1.09 (0.99 to 1.20)			

Notes:

[13] - Notes:
For the A/H3N2 Strain the N= 1651

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point description:

Objective 2a - GMTs were assessed at Day 1 and Day 29/57 for the 4 vaccine strains, using cell-derived target viruses, as measured by:
- HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains
- MN assay for the A/H3N2 strain

Dataset used: PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092[14]	575[15]		
Units: GMT				
number (confidence interval 95%)				
A/H1N1 Day 1 GMT	13.5 (12.01 to 15.14)	12.8 (11.06 to 14.72)		
A/H1N1 Day 29/57 GMT	78.0 (70.75 to 86.03)	57.3 (50.76 to 64.63)		
A/H3N2 Day 1 GMT	10.3 (9.53 to 11.15)	10.1 (9.15 to 11.10)		
A/H3N2 Day 29/57 GMT	23.1 (21.21 to 25.12)	23.9 (21.57 to 26.57)		
B/Yamagata Day 1 GMT	7.9 (7.38 to 8.51)	7.7 (7.04 to 8.39)		
B/Yamagata Day 29/57 GMT	35.6 (32.93 to 38.58)	26.0 (23.54 to 28.63)		
B/Victoria Day 1 GMT	7.7 (7.21 to 8.17)	7.8 (7.26 to 8.48)		
B/Victoria Day 29/57 GMT	22.4 (20.70 to 24.19)	19.6 (17.81 to 21.58)		

Notes:

[14] - N=1078 for A/H3N2 Strain

[15] - N=572 for A/H3N2 Strain

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMT ratio for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMT ratio for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point description:

Objective 2b - The GMT ratio was defined as the geometric mean of the postvaccination (28 days after last vaccination) HAI or MN titre for the US-licensed QIV divided by the geometric mean of the postvaccination HAI or MN titre for QIVc.
Dataset used: PPS

The GMT ratio for QIVc and the US-licensed QIV for each of the 4 vaccine strains using cell-derived target viruses were co-primary endpoints of the study and are presented in the Primary Immunogenicity endpoints section.

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects

End point values	GMT Ratio (US-licensed QIV/QIVc)			
Subject group type	Subject analysis set			
Number of subjects analysed	1667[16]			
Units: GMT Ratio				
number (confidence interval 95%)				
A/H1N1	0.73 (0.65 to 0.84)			
A/H3N2	1.04 (0.93 to 1.16)			
B/Yamagata	0.73 (0.66 to 0.81)			
B/Victoria	0.88 (0.79 to 0.97)			

Notes:

[16] - The A/H3N2 strain N= 1650

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 measured by MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMTs at Day 1 and Day 29/57 measured by MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point description:

Objective 3a - GMTs were assessed at Day 1 and Day 29/57 for 3 of the vaccine strains, using cell-derived target viruses in a subset of subjects as measured by:

- MN assay for the A/H1N1, B/Yamagata, and B/Victoria strains

Dataset used: Randomly selected subset (20%) of the PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[17]	122[18]		
Units: GMT				
geometric mean (confidence interval 95%)				
A/H1N1 Day 1 GMT	20.0 (14.58 to 27.50)	21.8 (15.39 to 30.81)		
A/H1N1 Day 29/57 GMT	137.3 (106.46 to 177.12)	105.8 (80.14 to 139.58)		
B/Yamagata Day 1 GMT	17.2 (14.51 to 20.36)	16.8 (13.97 to 20.23)		
B/Yamagata Day 29/57 GMT	57.4 (41.41 to 69.50)	51.7 (41.91 to 63.70)		
B/Victoria Day 1 GMT	11.5 (9.82 to 13.52)	11.1 (9.33 to 13.25)		
B/Victoria Day 29/57 GMT	21.7 (18.45 to 25.53)	18.5 (15.47 to 22.06)		

Notes:

[17] - Subset of the PPS

[18] - Subset of the PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMT ratio based on MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMT ratio based on MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point description:

Objective 3b - The GMT ratio was defined as the geometric mean of the postvaccination (28 days after last vaccination) MN titre for the US-licensed QIV divided by the geometric mean of the postvaccination MN titre for QIVc.

Dataset used: Randomly selected subset (20%) of the PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects

End point values	GMT Ratio (US-licensed QIV/QIVc)			
Subject group type	Subject analysis set			
Number of subjects analysed	317			
Units: GMT Ratio				
number (confidence interval 95%)				
A/H1N1	0.77 (0.56 to 1.06)			
B/Yamagata	0.90 (0.71 to 1.15)			
B/Victoria	0.85 (0.69 to 1.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with solicited AEs within 7 days after each study vaccination

End point title	Secondary Safety: Percentage of subjects with solicited AEs within 7 days after each study vaccination

End point description:

The secondary safety objective was to evaluate the safety and reactogenicity of QIVc and US-licensed QIV via (3) secondary safety endpoints; the first such endpoint was evaluating the percentage of subjects with at least one solicited AEs Day 1 through Day 7 after any study vaccination.

Dataset used: Solicited Safety Set = Randomised subjects who received study vaccine and had any assessment of solicited AEs and/or assessment of any use of analgesics/antipyretics.

End point type	Secondary

End point timeframe:

7 days after vaccination on Day 1 for previously vaccinated subjects and 7 days after vaccination on Day 1 and Day 29 for not previously vaccinated subjects

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	805		
Units: Percentage of Subjects				
number (not applicable)				
Solicited AEs	60.1	62.6		
Solicited Local AEs	41.9	44.6		
Solicited Systemic AEs	43.5	45.7		
Analgesic/Antipyretic Use	15.3	17.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)

End point title	Secondary Safety: Percentage of subjects with any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)

End point description:

The secondary safety objective was to evaluate the safety and reactogenicity of QIVc and US-licensed QIV via (3) secondary safety endpoints; the second such endpoint was evaluating the percentage of subjects with any unsolicited AEs from Day 1 to Day 29 in previously vaccinated subjects and from Day 1 to Day 57 in not previously vaccinated subjects.

Related AEs = considered at least possibly related to study vaccination by the investigator
Severity = based on the greatest severity associated with a preferred term per reported AE

Dataset used: Unsolicited Safety Set = Randomised subjects who received study vaccine and had any assessment of unsolicited AEs

End point type	Secondary

End point timeframe:

Day 1 to Day 29 for previously vaccinated subjects and Day 1 to Day 57 for those not previously vaccinated

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597	805		
Units: Percentage of Subjects				
number (not applicable)				
Any AE	26.2	25.7		
Any AE (Mild)	19.3	20.4		
Any AE (Moderate)	6.1	5.1		
Any AE (Severe)	0.8	0.2		
Related AE	4.4	4.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Safety: Percentage of subjects with any SAEs, New Onset of Chronic Disease (NOCD), or AEs leading to withdrawal during the study period from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for those who were not

End point title	Secondary Safety: Percentage of subjects with any SAEs, New Onset of Chronic Disease (NOCD), or AEs leading to withdrawal during the study period from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for those who were not

End point description:

The secondary safety objective evaluated the safety and reactogenicity of QIVc and US-licensed QIV via (3) secondary safety endpoints; this 3rd endpoint evaluated the percentage of subjects with any SAE, New Onset of Chronic Disease (NOCD), or AE leading to withdrawal during the study period from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for those who were not.

Definition(s):
SAEs = AEs defined as any untoward medical occurrence that at any dose resulted in one or more of the following: 1. Death, 2. Life-threatening 3. Required/prolonged hospitalization 4. Persistent or significant disability/incapacity 5. congenital anomaly/or birth defect 6. An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above

End point type	Secondary

End point timeframe:

Day 1 to Day 181 for previously vaccinated subjects and Day 1 to Day 209 for not previously vaccinated subjects

Dataset used: Unsolicited Safety Set = Randomised subjects who received study vaccine and had any assessment of unsolicited AEs

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1597[19]	805[20]		
Units: Percentage of Subjects				
number (not applicable)				
SAE	0.9	0.9		
Related SAE	0	0		
AE leading to study withdrawal	0.2	0		
NOCD	1.4	1.6		
Death	0.1	0		

Notes:

[19] - QIVc Unsolicited Safety Set

[20] - US-licensed QIV Unsolicited Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMR for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg-derived target viruses

End point title	Secondary Immunogenicity: GMR for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using egg- derived target viruses

End point description:

Objective 1c - The Geometric Mean Ratio (GMR) was defined as the fold increase in serum HAI or MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1) HAI or MN GMT

Dataset used: PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092	575		
Units: Ratio				
number (confidence interval 95%)	2.14 (1.98 to 2.31)	2.33 (2.13 to 2.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMR for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMR for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell- derived target viruses

End point description:

Objective 2c - The GMR was defined as the fold increase in serum HAI or MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1) HAI or MN GMT

Dataset used: PPS

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1092	575		
Units: Ratio				
number (confidence interval 95%)	4.12 (3.79 to 4.47)	3.03 (2.74 to 3.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity: GMR based on MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point title	Secondary Immunogenicity: GMR based on MN assay for 3 vaccine strains in a subset of subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV, using cell-derived target viruses

End point description:

Objective 3c - The GMR was defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1) MN GMT

Dataset used: Randomly selected subset (20%) of the PPS.

End point type	Secondary

End point timeframe:

28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)

End point values	QIVc	US-licensed QIV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	122		
Units: Ratio				
number (confidence interval 95%)	3.14 (2.56 to 3.85)	2.86 (2.28 to 3.57)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: Day 1 to end of study (Day 1 to Day 181 for previously vaccinated subjects; Day 1 to Day 209 for those not previously vaccinated
Nonserious Unsolicited AEs: Day 1 to Day 29 for previously vaccinated subjects; Day 1 to Day 57 for those who were not

Adverse event reporting additional description:

Nonserious Unsolicited AEs and SAEs are reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	QIVc

Reporting group description:

Randomised subjects who received QIVc and had any assessment of unsolicited AEs

Reporting group title	US-licensed QIV

Reporting group description:

Randomised subjects who received the US-licensed QIV and had any assessment of unsolicited AEs

Serious adverse events	QIVc	US-licensed QIV	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 1597 (0.94%)	7 / 805 (0.87%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 1597 (0.13%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			

subjects affected / exposed	0 / 1597 (0.00%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 1597 (0.00%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	2 / 1597 (0.13%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Ligamentitis			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (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			
Bronchiolitis			
subjects affected / exposed	1 / 1597 (0.06%)	3 / 805 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 1597 (0.19%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 1597 (0.06%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of eyelid			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral encephalitis			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterovirus infection			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 1597 (0.00%)	1 / 805 (0.12%)	
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	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 1597 (0.06%)	0 / 805 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 1597 (0.06%)	1 / 805 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	QIVc	US-licensed QIV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	416 / 1597 (26.05%)	207 / 805 (25.71%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	416 / 1597 (26.05%)	207 / 805 (25.71%)	
occurrences (all)	771	358	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2018	Version 1.0 to Version 2.0 The main reasons for the protocol amendment were the following: 1. A request from CBER that noninferior immune responses be assessed for all 8 co-primary endpoints, using MN assay data for the co-primary endpoints related to the A/H3N2 strain in addition to HAI assay data for the co-primary endpoints related to the A/H1N1, B/Yamagata, and B/Victoria strains. 2. Revision of the secondary immunogenicity objectives to specify that cell-derived target viruses would be used for the HAI and MN assays, and an exploratory objective was added to assess in a subset of subjects the immunogenicity of both vaccines using egg- derived target viruses in the HAI and MN assays. 3. A new description of Afluria as the QIV comparator and not the "US-licensed QIV" as FDA approval for its use in children 6 months and older had been delayed. 4. Clarification of the amount of blood to be collected from the subjects who consent to CMI evaluation in addition to immunogenicity evaluation.
17 May 2019	Version 2.0 to Version 3.0 The main reasons for the protocol amendment were the following: 1. Primary objective, specifying that cell-derived target viruses would be used in the HAI (A/H1N1, B/Yamagata, and B/Victoria) and MN (A/H3N2) assays for the primary immunogenicity endpoints of noninferiority. 2. Specification that the secondary immunogenicity objectives to assess immunogenicity using both cell-derived and egg-derived viruses in the HAI and MN assays will be done for the entire study population and not just a subset. 3. Changes to the statistical parameters defining seroconversion and noninferiority of GMT ratio for A/H3N2 using the MN assay. 4. Addition of an exploratory endpoint to assess the immunogenicity of A/H3N2 by the HAI assay using cell-derived and egg-derived target viruses, as recent data suggested that strains of this A subtype were able to agglutinate red blood cells. 5. Classification of the CMI Population as a separate group in the protocol and not a subset of the Immunogenicity Group. Initially, subjects undergoing CMI evaluation were to have 12 mL of blood collected (versus 8 mL for immunogenicity testing only) to allow for both CMI and immunogenicity evaluation. Upon further consideration of the burden the larger blood volume imposed upon subjects in this pediatric age group, a change was made so that all subjects in the study would have the same total amount of blood drawn. Therefore, the CMI Population formed a separate group of approximately 84 subjects whose samples were used primarily for the evaluation of antigen-stimulated T-cell responses with the possibility of limited antibody-specific assessment for bridging purposes to the larger Immunogenicity Group. 6. Revision in the protocol text to describe the comparator vaccine as the "US-licensed QIV". Afluria Quadrivalent, the comparator influenza vaccine, was now licensed for use in children aged 6 months and older in the US (approved October 2018).

09 December 2019	Version 3.0 to Version 4.0 The main reason for the third protocol amendment was to accelerate preparation of the CSR and facilitate timely submission of the supplemental BLA. The final analysis of the primary and secondary immunogenicity endpoints would be conducted once all subjects had completed all immunogenicity assessments, which was at the end of the treatment period (ie, up to 28 days following the last vaccination). The analysis of all solicited AEs and unsolicited AEs reported during the treatment period would also be performed. The changes included the following: 1. Wording added to the protocol synopsis and text explaining that the final analysis of the primary and secondary immunogenicity endpoints would be conducted once all subjects had completed all immunogenicity assessments (end of treatment period, ie, up to 28 days following last vaccination dose). At this time, the analysis of all solicited AEs and of unsolicited AEs reported during the treatment period would also be conducted. 2. Addition to the protocol text to describe Procedures for Database Lock and Unblinding of Randomization Code at the end of the treatment period. 3. Correction that screening procedures included collection of prior and concomitant medications or vaccinations taken up to 1 month prior to start of study and not 2 months, which was a typographical error. 4. Addition of ESP term (External Service Provider) to the Protocol and List of Abbreviations; End of Study definition was also added to the List of Definitions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported