Clinical trial results:
A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study to Evaluate Safety and Immunogenicity of Cell-Based Quadrivalent Subunit Influenza Virus Vaccine and Cell-Based Trivalent Subunit Influenza Virus Vaccines in Subjects Ages >=4 Years to <18 Years.

Summary

EudraCT number	2015-000133-70
Trial protocol	Outside EU/EEA
Global end of trial date	19 August 2014

Results information

Result version number	v1 (current)
This version publication date	08 July 2016
First version publication date	01 March 2015

Trial information

Trial identification

Sponsor protocol code	V130_03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01992107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics, Inc
Sponsor organisation address	350 Massachusetts Ave, Cambridge, MA, United States, 02139
Public contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Immunogenicity Objective

- To demonstrate noninferiority of antibody responses of Quadrivalent Subunit Influenza Virus Vaccine (QIVc) to comparator Trivalent Subunit Influenza Virus Vaccine (TIVc) in subjects >=4 to <18 years of age , as assessed by the ratio of geometric mean titer (GMT) for each of the 4 vaccine strains separately after vaccination.
- To demonstrate noninferiority of antibody responses of QIVc to comparator TIVc after vaccination in subjects >=4 to <18 years of age, as assessed by differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination.

The study was considered a success -as both co-primary immunogenicity objectives were achieved.

Protection of trial subjects:

This trial was performed with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, the applicable regulatory requirements(s) for the country in which the study is conducted, and applicable standard operating procedures (SOPs

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 2333
Worldwide total number of subjects	2333
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)	0
Children (2-11 years)	1588
Adolescents (12-17 years)	745
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 90 centers in the United States (US)

Pre-assignment

Screening details:

All enrollled subjects were included in the trial

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QIVc (≥4 to <18 years)

Arm description:

Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)

Arm type	Experimental
Investigational medicinal product name	Influenza Virus Vaccine (cell-derived seasonal quadrivalent) [2013/2014] thimerosal free)
Investigational medicinal product code	V130
Other name	QIVc (quadrivalent influenza vaccine)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL

Arm title	TIV1c (≥4 to <18 years)

Arm description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season

Arm type	Active comparator
Investigational medicinal product name	Influenza Virus Vaccine (cell-derived seasonal Trivalent) [2013/2014] thimerosal free)
Investigational medicinal product code	TIV1c
Other name	TIV1c (trivalent influenza vaccine)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL

Arm title	TIV2c (≥4 to <18 years)

Arm description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014

Arm type	Active comparator

Investigational medicinal product name	Influenza Virus Vaccine (cell-derived seasonal trivalent) [2013/2014] thimerosal free)
Investigational medicinal product code	TIV2c
Other name	TIV2c (trivalent influenza vaccine)
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL

Number of subjects in period 1	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)
Started	1159	593	581
Completed	1091	560	545
Not completed	68	33	36
Consent withdrawn by subject	13	7	8
Adverse event, non-fatal	-	1	-
Other	7	3	2
Administrative reasons	2	-	-
Lost to follow-up	46	22	26

Baseline characteristics

Reporting groups	
Reporting group title	QIVc (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)	
Reporting group title	TIV1c (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season	
Reporting group title	TIV2c (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014	

Reporting group values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)
Number of subjects	1159	593	581
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	9.5	9.5	9.3
standard deviation	± 3.8	± 3.8	± 3.7
Gender categorical Units: Subjects			
Female	556	284	284
Male	603	309	297

Reporting group values	Total		
Number of subjects	2333		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		

Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	1124		
Male	1209		

End points

End points reporting groups

Reporting group title	QIVc (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)	
Reporting group title	TIV1c (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season	
Reporting group title	TIV2c (≥4 to <18 years)
Reporting group description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014	
Subject analysis set title	TIV1c_First Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season	
Subject analysis set title	QIVc _First Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)	
Subject analysis set title	TIV2c _First Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014	
Subject analysis set title	QIVc _Second Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)	
Subject analysis set title	TIV1c_Second Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season	
Subject analysis set title	TIV2c _Second Vaccine (≥4 to <6 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014	
Subject analysis set title	QIVc _First Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)	
Subject analysis set title	TIV1c_First Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2,B1) recommended for 2013-2014 season	
Subject analysis set title	TIV1c_Second Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season

Subject analysis set title	QIVc _Second Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)

Subject analysis set title	TIV2c _First Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014

Subject analysis set title	TIV1c (≥9 to <18 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season

Subject analysis set title	QIVc (≥9 to <18 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)

Subject analysis set title	TIV2c _Second Vaccine (≥6 to <9 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014

Subject analysis set title	TIV2c (≥9 to <18 years)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014

Primary: 1.Geometric Mean Titre (GMT) in subjects after receiving one or two doses of either QIVc, TIV1c or TIV2c

End point title	1.Geometric Mean Titre (GMT) in subjects after receiving one or two doses of either QIVc, TIV1c or TIV2c

End point description:

Immunogenicity of QIVc to comparator TIVc (For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c) was assessed in terms of ratios of GMT in subjects (Previously vaccinated and Not previously vaccinated) measured by hemagglutination inhibition (HI) assay, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c

End point type	Primary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Titers				
geometric mean (confidence interval 95%)				
H1N1: Day 1 (N=1014, 510)	96 (86 to 107)	100 (86 to 116)	0 (0 to 0)	
H1N1: Day 22/Day 50 (N=1014, 510)	1090 (1027 to 1157)	1125 (1034 to 1224)	0 (0 to 0)	
H3N2: Day 1 (N=1013, 510)	206 (188 to 225)	196 (172 to 222)	0 (0 to 0)	
H3N2: Day 22/Day 50 (N=1013, 510)	738 (703 to 774)	776 (725 to 831)	0 (0 to 0)	
B1: Day 1 (N=1013, 510)	26 (24 to 28)	23 (21 to 26)	0 (0 to 0)	
B1: Day 22/Day 50 (N=1013, 510)	155 (146 to 165)	154 (141 to 168)	0 (0 to 0)	
B2: Day 1(N=1009, 501)	23 (21 to 25)	0 (0 to 0)	23 (21 to 26)	
B2: Day 22/Day 50 (N=1013, 501)	185 (171 to 200)	0 (0 to 0)	185 (166 to 207)	

Statistical analyses

Statistical analysis title	1.Non-inferiority testing geometric mean titer

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c, assessed in terms of ratios of GMT against influenza strain H1N1

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.14
Variability estimate	Standard deviation

Notes:

[1] - Non-inferiority was established if the upper bound of the two-sided 95% confidence interval (CI) for the ratio of GMTs (GMT TIV1c/GMT QIVc) for HI antibody does not exceed the non-inferiority margin of 1.5

Statistical analysis title	2. Non-inferiority testing geometric mean titer

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c, assessed in terms of ratios of GMT against influenza strain H3N2

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)

Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.14
Variability estimate	Standard deviation

Notes:

[2] - Non-inferiority was established if the upper bound of the two-sided 95% confidence interval (CI) for the ratio of GMTs (GMT TIV1c/GMT QIVc) for HI antibody does not exceed the non-inferiority margin of 1.5

Statistical analysis title	3.Non-inferiority testing geometric mean Titer

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c, assessed in terms of ratios of GMT against influenza strain B1

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.1
Variability estimate	Standard deviation

Notes:

[3] - Non-inferiority was established if the upper bound of the two-sided 95% confidence interval (CI) for the ratio of GMTs (GMT TIV1c/GMT QIVc) for HI antibody does not exceed the non-inferiority margin of 1.5

Statistical analysis title	4. Non-inferiority testing geometric mean Titer

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c, assessed in terms of ratios of GMT against influenza strain B2

Comparison groups	QIVc (≥4 to <18 years) v TIV2c (≥4 to <18 years)
Number of subjects included in analysis	1740
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANCOVA
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.14
Variability estimate	Standard deviation

Notes:

[4] - Non-inferiority was established if the upper bound of the two-sided 95% confidence interval (CI) for the ratio of GMTs (GMT TIV1c/GMT QIVc) for HI antibody does not exceed the non-inferiority margin of 1.5

Primary: 2.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2c

End point title	2.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2c

End point description:

Immunogenicity of QIVc to comparator TIVc (For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c) was assessed in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing seroconversion or significant increase in HI antibody titers, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
Seroconversion is defined in subjects seronegative at baseline (i.e., HI titer <1:10 at Day 1) as postvaccination HI titer ≥1:40, and defined in subjects seropositive at baseline (i.e., HI titer ≥1:10 at Day 1) as a minimum of a 4-fold increase in post-vaccination HI titer.

End point type	Primary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1: Day 22/Day 50 (N=1014,510)	72 (69 to 75)	75 (70 to 78)	0 (0 to 0)	
H3N2: Day 22/Day 50 (N=1013, 510)	47 (44 to 50)	51 (46 to 55)	0 (0 to 0)	
B1: Day 22/Day 50 (N=1013,510)	66 (63 to 69)	66 (62 to 70)	0 (0 to 0)	
B2: Day 22/Day 50 (N=1009,501)	73 (70 to 76)	0 (0 to 0)	71 (67 to 75)	

Statistical analyses

Statistical analysis title	1.Non-inferiority testing SC rates of QIVc to TIVc

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c in terms of differences in seroconversion rates against influenza strain H1N1

Comparison groups	TIV1c (≥4 to <18 years) v QIVc (≥4 to <18 years)

Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	ANCOVA
Parameter estimate	Difference b/w SC rates (Day 22/Day 50)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	6.9
Variability estimate	Standard deviation

Notes:

[5] - Non-inferiority was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c – % seroconversion QIVc) for HI antibody does not exceed the margin of 10%

Statistical analysis title	2.Non-inferiority testing SC rates of QIVc to TIVc

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c in terms of differences in seroconversion rates against influenza strain H3N2

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANCOVA
Parameter estimate	Difference b/w SC rates (Day 22/Day 50)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	9.2
Variability estimate	Standard deviation

Notes:

[6] - Non-inferiority was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c – % seroconversion QIVc) for HI antibody does not exceed the margin of 10%

Statistical analysis title	3.Non-inferiority testing SC rates of QIVc to TIVc

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c in terms of differences in seroconversion rates against influenza strain B1

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANCOVA
Parameter estimate	Difference b/w SC rates (Day 22/Day 50)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	4.5
Variability estimate	Standard deviation

Notes:

[7] - Non-inferiority was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c – % seroconversion QIVc) for HI antibody does not exceed the margin of 10%

Statistical analysis title	4.Non-inferiority testing SC rates of QIVc to TIVc

Statistical analysis description:

Non-inferiority of immune responses of QIVc to TIV1c in terms of differences in seroconversion rates against influenza strain B2

Comparison groups	QIVc (≥4 to <18 years) v TIV2c (≥4 to <18 years)
Number of subjects included in analysis	1740
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Method	ANCOVA
Parameter estimate	Difference b/w SC rates (Day 22/Day 50)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	3.2
Variability estimate	Standard deviation

Notes:

[8] - Non-inferiority was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c – % seroconversion QIVc) for HI antibody does not exceed the margin of 10%

Secondary: 3.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2 c in ≥4 to <18 years

End point title	3.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2 c in ≥4 to <18 years

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing seroconversion or significant increase in HI antibody titers, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c
Seroconversion is defined in subjects seronegative at baseline (i.e., HI titer <1:10 at Day 1) as post-vaccination HI titer ≥1:40, and defined in subjects seropositive at baseline (i.e., HI titer ≥1:10 at Day 1) as a minimum of a 4-fold increase in post-vaccination HI titer.
The Center for Biologics Evaluation, Research, and Review (CBER) criterion for an adult population is that the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1: Day 22 or Day 50 (N=1113,566)	73 (70 to 76)	74 (70 to 77)	0 (0 to 0)	
H3N2: Day 22 or Day 50 (N=1112,566)	47 (44 to 50)	51 (47 to 55)	0 (0 to 0)	
B1: Day 22 or Day 50 (N=1112,566)	67 (64 to 70)	66 (61 to 69)	0 (0 to 0)	
B2: Day 22 or Day 50 (N=1108,566)	73 (70 to 76)	0 (0 to 0)	72 (68 to 76)	

Statistical analyses

No statistical analyses for this end point

Secondary: 4.Number (%) of subjects achieving HI titer ≥1:40 after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point title	4.Number (%) of subjects achieving HI titer ≥1:40 after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing HI titer ≥1:40, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c
The CBER criterion for adult population is that the lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 70%

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1: Day 1(N=1113,566)	76 (73 to 78)	79 (75 to 82)	0 (0 to 0)	
H1N1: Day 22 or Day 50(N=1113,566)	99 (98 to 100)	99 (98 to 100)	0 (0 to 0)	
H3N2: Day 1(N=1112,566)	90 (88 to 91)	89 (86 to 92)	0 (0 to 0)	
H3N2: Day 22 or Day 50(N=1112,566)	100 (99 to 100)	99 (98 to 100)	0 (0 to 0)	
B1: Day 1(N=1112,566)	49 (46 to 52)	45 (41 to 49)	0 (0 to 0)	
B1: Day 22 or Day 50(N=1112,566)	92 (91 to 94)	93 (90 to 95)	0 (0 to 0)	
B2: Day 1(N=1108,556)	46 (43 to 49)	0 (0 to 0)	47 (43 to 51)	
B2: Day 22 or Day 50(N=1108,556)	91 (89 to 93)	0 (0 to 0)	91 (88 to 93)	

Statistical analyses

No statistical analyses for this end point

Secondary: 5.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point title	5.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing seroconversion or significant increase in HI antibody titers, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c
Seroconversion is defined in subjects seronegative at baseline (i.e., HI titer <1:10 at Day 1) as post-vaccination HI titer ≥1:40, and defined in subjects seropositive at baseline (i.e., HI titer ≥1:10 at Day 1) as a minimum of a 4-fold increase in post-vaccination HI titer.
The Committee for Medicinal Products for Human Use (CHMP) criterion for adult population is that the percentage of subjects with seroconversion or significant increase in HI antibody is >40%

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1: Day 22/Day 50(N=1113,566)	73 (70 to 76)	74 (70 to 77)	0 (0 to 0)	
H3N2: Day 22/Day 50(N=1112,566)	47 (44 to 50)	51 (47 to 55)	0 (0 to 0)	
B1: Day 22/Day 50(N=1112,566)	67 (64 to 70)	66 (61 to 69)	0 (0 to 0)	
B2: Day 22/Day 50(N=1108,556)	73 (70 to 76)	0 (0 to 0)	72 (68 to 76)	

Statistical analyses

No statistical analyses for this end point

Secondary: 6.Number (%) of subjects achieving HI titer ≥1:40 after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point title	6.Number (%) of subjects achieving HI titer ≥1:40 after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years

End point description:

Immunogenicity was assessed in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing HI titer ≥1:40, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c
The CHMP criterion for an adult population is that the percentage of subjects achieving an HI titer ≥1:40 is >70%

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Percentages Of subjects				
number (confidence interval 95%)				
H1N1: Day 1(N=1113,566)	76 (73 to 78)	79 (75 to 82)	0 (0 to 0)	
H1N1: Day 22/Day 50(N=1113,566)	99 (98 to 100)	99 (98 to 100)	0 (0 to 0)	
H3N2: Day 1(N=1112,566)	90 (88 to 91)	89 (86 to 92)	0 (0 to 0)	
H3N2: Day 22/Day 50(N=1112,566)	100 (99 to 100)	99 (98 to 100)	0 (0 to 0)	
B1: Day 1(N=1112,566)	49 (46 to 52)	45 (41 to 49)	0 (0 to 0)	
B1: Day 22/Day 50(N=1112,566)	92 (91 to 94)	93 (90 to 95)	0 (0 to 0)	
B2: Day 1(N=1108,556)	46 (43 to 49)	0 (0 to 0)	47 (43 to 51)	
B2: Day 22/Day 50(N=1108,556)	91 (89 to 93)	0 (0 to 0)	91 (88 to 93)	

Statistical analyses

No statistical analyses for this end point

Secondary: 7.Geometric mean ratios (GMR) in subjects after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years age

End point title	7.Geometric mean ratios (GMR) in subjects after one or two doses of either QIVc, TIV1c or TIV2c in ≥4 to <18 years age

End point description:

Immunogenicity was measured in subjects (Previously vaccinated and Not previously vaccinated) as the geometric mean ratio (GMR). The ratio of postvaccination to prevaccination HI GMTs, three weeks after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c
For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c
The CHMP criterion for GMR in adult population is >2.5

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Ratio				
geometric mean (confidence interval 95%)				
A/H1N1: TIV1c/QIVc [Day 22 (Day 50)/Day1]	11 (10 to 13)	12 (10 to 13)	0 (0 to 0)	
A/H3N2: TIV1c/QIVc [Day 22 (Day 50)/Day1]	3.65 (3.4 to 3.91)	3.97 (3.59 to 4.38)	0 (0 to 0)	
B1: TIV1c/QIVc [Day 22 (Day 50)/Day1]	6.15 (5.72 to 6.61)	6.24 (5.64 to 6.91)	0 (0 to 0)	
B2: TIV2c/QIVc [Day 22 (Day 50)/Day1]	8.17 (7.5 to 8.89)	0 (0 to 0)	8.45 (7.5 to 9.53)	

Statistical analyses

No statistical analyses for this end point

Secondary: 8.GMT in subjects after receiving one or two doses of either QIVc, TIV1c against B2 strain

End point title	8.GMT in subjects after receiving one or two doses of either QIVc, TIV1c against B2 strain[9]

End point description:

Immunogenicity of QIVc to comparator TIV1c was assessed in terms of ratios of GMT in subjects (Previously vaccinated and Not previously vaccinated) measured by HI assay, three weeks after last vaccination with one or two doses of either QIVc or TIV1c
Superiority was established if the upper bound of the two-sided 95% CI for the ratio of GMTs (GMT TIV1c /GMT QIVc) for HI antibody does not exceed the superiority margin of 1

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

Notes:

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

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1159	593		
Units: Titers				
geometric mean (confidence interval 95%)				
Day1(N=1108,563)	22 (20 to 24)	21 (18 to 23)		
Day 22/Day 50(N=1108,563)	176 (164 to 189)	45 (41 to 49)		

Statistical analyses

Statistical analysis title	Superiority of QIVc to TIV1c regarding B2 antibody
Statistical analysis description:	
Superiority of immune responses of QIVc to TIV1c in terms of ratios of GMT against influenza strain B2	
Comparison groups	TIV1c (≥4 to <18 years) v QIVc (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.29
Variability estimate	Standard deviation

Secondary: 9.Number (%) of subjects achieving seroconversion against B2 strain after one or two doses of either QIVc or TIV1c

End point title	9.Number (%) of subjects achieving seroconversion against B2 strain after one or two doses of either QIVc or TIV1c[10]
End point description:	
Immunogenicity of QIVc to comparator TIV1c in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing seroconversion or significant increase in HI antibody titers, against influenza strain B2, three weeks after last vaccination with QIVc or TIV1c Superiority criterion was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c – % seroconversion QIVc) for HI antibody does not exceed the margin of 0 points	
End point type	Secondary
End point timeframe:	
Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)	
Notes:	
[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics only for applicable arms	

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1159	593		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 22/Day 50(N=1108,563)	73 (70 to 76)	26 (23 to 30)		

Statistical analyses

Statistical analysis title	superiority of QIVc to TIV1c regarding B2 antibody

Statistical analysis description:

Superiority of immune responses of QIVc to TIV1c in terms of seroconversion rates against influenza strain B2

Comparison groups	QIVc (≥4 to <18 years) v TIV1c (≥4 to <18 years)
Number of subjects included in analysis	1752
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference b/w SC rates(Day 22/Day 50)
Point estimate	-47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.1
upper limit	-42.1
Variability estimate	Standard deviation

Secondary: 10.GMT in subjects after receiving one or two doses of either QIVc, TIV2c against B1 strain

End point title	10.GMT in subjects after receiving one or two doses of either QIVc, TIV2c against B1 strain[11]

End point description:

Immunogenicity of QIVc to comparator TIV2c was assessed in terms of ratios of GMT in subjects (Previously vaccinated and Not previously vaccinated) measured by HI assay, three weeks after last vaccination with one or two doses of either QIVc or TIV2c
Superiority was established if the upper bound of the two-sided 95% CI for the ratio of GMTs (GMT TIV2c /GMT QIVc) for HI antibody does not exceed the superiority margin of 1

End point type	Secondary

End point timeframe:

Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)

Notes:

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

End point values	QIVc (≥4 to <18 years)	TIV2c (≥4 to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1159	581		
Units: Titers				
geometric mean (confidence interval 95%)				

Day1(N=1112,557) Day 22/Day 50(N=1112,557)	25 (23 to 27) 154 (145 to 163)	24 (22 to 27) 59 (54 to 64)		

Statistical analyses

Statistical analysis title	Superiority of QIVc to TIV2c regarding B1 antibody
Statistical analysis description: Superiority of immune responses of QIVc to TIV2c in terms of ratios of GMT against influenza strain B1	
Comparison groups	QIVc (≥4 to <18 years) v TIV2c (≥4 to <18 years)
Number of subjects included in analysis	1740
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Ratios of GMT (Day 22/Day 50)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.42
Variability estimate	Standard deviation

Secondary: 11.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc or TIV2c

End point title	11.Number (%) of subjects achieving seroconversion after one or two doses of either QIVc or TIV2c[12]
End point description: Immunogenicity of QIVc to comparator TIV2c in terms of number (%) of subjects (Previously vaccinated and Not previously vaccinated) showing seroconversion or significant increase in HI antibody titers, against influenza strain B1, three weeks after last vaccination with QIVc or TIV2c Superiority was established if the upper bound of the two-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV2c – % seroconversion QIVc) for HI antibody does not exceed the margin of 0 points	
End point type	Secondary
End point timeframe: Three weeks post vaccination (Day 22 for previously vaccinated and Day 50 for Not previously vaccinated subjects)	
Notes: [12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Statistics only for applicable arms	

End point values	QIVc (≥4 to <18 years)	TIV2c (≥4 to <18 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1159	581		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 22/Day 50(N=1112,557)	67 (64 to 70)	33 (29 to 37)		

Statistical analyses

Statistical analysis title	superiority of QIVc to TIV2c regarding B1 antibody
Statistical analysis description:	
Superiority of immune responses of QIVc to TIV2c in terms of seroconversion rates against influenza strain B1	
Comparison groups	QIVc (≥4 to <18 years) v TIV2c (≥4 to <18 years)
Number of subjects included in analysis	1740
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference b/w SC rates(Day 22/Day 50)
Point estimate	-34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.8
upper limit	-29.3
Variability estimate	Standard deviation

Secondary: 12.Number of subjects reporting solicited adverse events (AEs) after one or two doses of either QIVc, TIV1c or TIV2c by age sub-strata

End point title	12.Number of subjects reporting solicited adverse events (AEs) after one or two doses of either QIVc, TIV1c or TIV2c by age sub-strata
End point description:	
Safety was assessed in terms of number of subjects (Previously vaccinated and Not previously vaccinated) reporting solicited local and systemic reactions, day 1 to 7 after last vaccination with one or two doses of either QIVc, TIV1c or TIV2c.For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c.	
End point type	Secondary
End point timeframe:	
Day 1 to 7 after last vaccination	

End point values	QIVc _First Vaccine (≥4 to <6 years)	TIV1c_First Vaccine (≥4 to <6 years)	TIV2c _First Vaccine (≥4 to <6 years)	QIVc _Second Vaccine (≥4 to <6 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	182	91	93	98
Units: Subjects				
Any local	103	51	47	52
Tenderness	83	41	40	49
Ecchymosis	16	10	7	6

Erythema	32	21	16	17
Induration	24	18	12	11
Pain	0	0	0	0
Any systemic	51	18	17	30
Change of eating habits	19	6	6	9
Sleepiness	34	11	9	13
Chills	10	2	1	4
Irritability	29	9	9	15
Nausea	0	0	0	0
Myalgia	0	0	0	0
Arthralgia	0	0	0	0
Headache	0	0	0	0
Fatigue	0	0	0	0
Vomiting	8	2	2	3
Diarrhea	8	2	2	3
Loss of appetite	0	0	0	0
Body temperature(>=38C)	7	4	3	4
Analgesics-Preventive	13	1	1	2
Analgesics-Treatment	12	4	3	2

End point values	TIV1c_Second Vaccine (≥4 to <6 years)	TIV2c _Second Vaccine (≥4 to <6 years)	QIVc _First Vaccine (≥6 to <9 years)	TIV1c_First Vaccine (≥6 to <9 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	47	372	185
Units: Subjects				
Any local	17	17	237	124
Tenderness	15	15	1	0
Ecchymosis	3	2	35	17
Erythema	3	7	83	43
Induration	2	4	59	35
Pain	0	0	201	105
Any systemic	9	9	117	67
Change of eating habits	3	1	0	0
Sleepiness	3	5	0	0
Chills	2	1	16	6
Irritability	6	6	0	0
Nausea	0	0	29	9
Myalgia	0	0	43	26
Arthralgia	0	0	13	10
Headache	0	0	52	24
Fatigue	0	0	47	26
Vomiting	0	0	12	6
Diarrhea	1	2	13	11
Loss of appetite	0	0	33	10
Body temperature(>=38C)	1	0	16	5
Analgesics-Preventive	1	0	14	6
Analgesics-Treatment	2	1	27	13

End point values	TIV2c _First Vaccine (≥6 to <9 years)	QIVc _Second Vaccine (≥6 to <9 years)	TIV1c_Second Vaccine (≥6 to <9 years)	TIV2c _Second Vaccine (≥6 to <9 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	186	205	112	116
Units: Subjects				
Any local	116	102	64	66
Tenderness	0	0	0	0
Ecchymosis	14	9	9	7
Erythema	38	29	17	19
Induration	24	25	18	12
Pain	107	95	61	62
Any systemic	65	46	30	27
Change of eating habits	0	0	0	0
Sleepiness	0	0	0	0
Chills	8	2	3	0
Irritability	0	0	0	0
Nausea	10	7	6	4
Myalgia	19	18	11	11
Arthralgia	7	6	5	4
Headache	23	9	8	7
Fatigue	33	18	12	10
Vomiting	6	7	2	1
Diarrhea	9	4	4	1
Loss of appetite	15	6	9	8
Body temperature(>=38C)	4	6	2	2
Analgesics-Preventive	8	7	4	4
Analgesics-Treatment	10	15	4	10

End point values	QIVc (≥9 to <18 years)	TIV1c (≥9 to <18 years)	TIV2c (≥9 to <18 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	579	294	282	
Units: Subjects				
Any local	377	175	156	
Tenderness	0	0	0	
Ecchymosis	24	16	13	
Erythema	110	51	43	
Induration	88	43	36	
Pain	334	150	142	
Any systemic	232	121	94	
Change of eating habits	0	0	0	
Sleepiness	0	0	0	
Chills	43	17	10	
Irritability	0	0	0	
Nausea	55	24	21	

Myalgia	94	50	41	
Arthralgia	36	19	22	
Headache	127	68	50	
Fatigue	104	46	44	
Vomiting	10	4	5	
Diarrhea	22	11	9	
Loss of appetite	51	25	25	
Body temperature(>=38C)	7	8	4	
Analgesics-Preventive	15	6	8	
Analgesics-Treatment	24	20	14	

Statistical analyses

No statistical analyses for this end point

Secondary: 13.Number of subjects reporting unsolicited adverse events (AEs) after one or two doses of either QIVc, TIV1c or TIV2c by overall age group

End point title	13.Number of subjects reporting unsolicited adverse events (AEs) after one or two doses of either QIVc, TIV1c or TIV2c by overall age group

End point description:

Safety was assessed in terms of number of subjects (Previously vaccinated and Not previously vaccinated) reporting unsolicited AEs (day 1 to 22 for Previously vaccinated and day 1 to day 50 for Not previously vaccinated subjects), serious adverse events (SAEs), medically attended AEs, AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), and concomitant medications (day 1 to day 181 for Previously vaccinated and day 1 to day 210 for Not previously vaccinated subjects) after receiving one or two doses of either QIVc, TIV1c or TIV2c. For H1N1, H3N2 and B1 strain, the comparison is between QIVc and TIV1c and for B2 i.e. alternate B strain, the comparison is between QIVc and TIV2c.

End point type	Secondary

End point timeframe:

Day 1 to 210 post vaccination

End point values	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)	TIV2c (≥4 to <18 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1159	593	581	
Units: Subjects				
Any AE	279	139	152	
Possibly/probably related AE	56	34	31	
SAE	6	7	2	
Possibly/probably related SAE	0	0	0	
AE leading to study withdrawal	0	1	0	
Medically attended AE	310	156	153	
NOCD	20	11	11	
Death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were collected from day 1 to day 181 for previously vaccinated subjects and day 1 to day 210 for not previously vaccinated subjects

Adverse event reporting additional description:

Solicited AEs were collected from day 1 to day 7 after last vaccination, unsolicited AEs were collected from day 1 to day 22 for previously vaccinated subjects and day 1 to day 50 for not previously vaccinated subjects.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	TIV2c (≥4 to <18 years)

Reporting group description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV2c that contains an alternate B strain compared to what is recommended for 2013-2014

Reporting group title	QIVc (≥4 to <18 years)

Reporting group description:

Subjects received one or two doses of cell derived quadrivalent influenza vaccine (QIVc)

Reporting group title	TIV1c (≥4 to <18 years)

Reporting group description:

Subjects received one or two doses of cell derived trivalent influenza vaccine TIV1c (H1N1, H3N2, B1) recommended for 2013-2014 season

Serious adverse events	TIV2c (≥4 to <18 years)	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 570 (0.35%)	6 / 1149 (0.52%)	7 / 579 (1.21%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hippocampal sclerosis			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction.			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 570 (0.18%)	0 / 1149 (0.00%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oppositional defiant disorder			
subjects affected / exposed	0 / 570 (0.00%)	1 / 1149 (0.09%)	0 / 579 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess of eyelid			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 570 (0.18%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 570 (0.00%)	0 / 1149 (0.00%)	1 / 579 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	TIV2c (≥4 to <18 years)	QIVc (≥4 to <18 years)	TIV1c (≥4 to <18 years)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	392 / 570 (68.77%)	840 / 1149 (73.11%)	417 / 579 (72.02%)
Nervous system disorders			
Headache			
subjects affected / exposed	88 / 570 (15.44%)	204 / 1149 (17.75%)	105 / 579 (18.13%)
occurrences (all)	111	264	132
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	315 / 570 (55.26%)	664 / 1149 (57.79%)	324 / 579 (55.96%)
occurrences (all)	376	789	381
Fatigue			
subjects affected / exposed	82 / 570 (14.39%)	165 / 1149 (14.36%)	82 / 579 (14.16%)
occurrences (all)	107	193	97
Chills			
subjects affected / exposed	21 / 570 (3.68%)	73 / 1149 (6.35%)	29 / 579 (5.01%)
occurrences (all)	23	81	31
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 570 (7.37%)	95 / 1149 (8.27%)	40 / 579 (6.91%)
occurrences (all)	51	110	44
Psychiatric disorders			
Eating disorders			

subjects affected / exposed	51 / 570 (8.95%)	115 / 1149 (10.01%)	49 / 579 (8.46%)
occurrences (all)	7	29	11
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	66 / 570 (11.58%)	150 / 1149 (13.05%)	84 / 579 (14.51%)
occurrences (all)	78	168	89
Arthralgia			
subjects affected / exposed	33 / 570 (5.79%)	63 / 1149 (5.48%)	35 / 579 (6.04%)
occurrences (all)	38	69	42

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2014	(1) inclusion of safety analysis based on age groups and time periods as detailed in SAP.(2) clarification regarding clinic visit and safety call visit windows.(3) correction of how the IRT system assigns Subject Identifiers.(4) correction of sequence for enrollment and randomization.(5) clarification on use of diary cards assigned to subject based on age at time of enrollment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported