Clinical trial results:
A Combined Phase II/III, Observer-Blind, Randomized, Multi-center Study to Evaluate Safety, Tolerability and Immunogenicity of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture or in Embryonated Hen Eggs (Fluvirin®), in Healthy Children and Adolescents Aged 3-17 Years

Summary

EudraCT number	2007-001534-13
Trial protocol	HU LT FI IT
Global end of trial date	17 July 2008

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	04 December 2014
Version creation reason	• Correction of full data set Required for the re-QC project because of the EudraCT system glitch and possible updates to results may be required. Moreover, a change in system user for this study is necessary.

Trial information

Trial identification

Sponsor protocol code	V58P12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00645411
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines, 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	30 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Co-Primary:
To demonstrate non-inferiority of the post-vaccination (Day 50) hemagglutination inhibition (HI) geometric mean titer (GMT) of the cell culture-derived influenza vaccine to the corresponding GMT of the egg-derived influenza vaccine for all three strains after two doses administered four weeks apart to a subset of children 3-8 years of age (Cohort 3, immunogenicity subset).
To demonstrate non-inferiority of the percentages of subjects achieving seroconversion or significant increase in antibody titer at Day 50 following administration of the cell culture-derived influenza vaccine to the corresponding percentages of subjects following administration of the egg-derived influenza vaccine for all three strains after two doses administered four weeks apart to a subset of children 3-8 years of age (Cohort 3, immunogenicity subset).

Protection of trial subjects:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines.
An oral temperature ≥38.0°C (≥100.4°F) or serious active infection was a reason for delaying vaccination.
Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	08 October 2007
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	Finland: 632
Country: Number of subjects enrolled	Italy: 149
Country: Number of subjects enrolled	Lithuania: 248
Country: Number of subjects enrolled	Hungary: 575
Country: Number of subjects enrolled	Croatia: 109
Country: Number of subjects enrolled	Romania: 3

Country: Number of subjects enrolled	United States: 1888
Worldwide total number of subjects	3604
EEA total number of subjects	1716

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)	3017
Adolescents (12-17 years)	587
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 14 sites in Finland, 16 in the US, 9 in Croatia, 5 in Italy, 6 in Lithuania, 2 in Romania, 8 in Hungary.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1+2 cTIV (9-17 years)

Arm description:

All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.

Arm type	Experimental
Investigational medicinal product name	Cell culture-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	cTIV, Optaflu
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Cohort 1+2 eTIV (9-17 years)

Arm description:

All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.

Arm type	Active comparator
Investigational medicinal product name	Egg-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	eTIV, Fluvirin
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Cohort 3 cTIV (3-8 years)

Arm description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

Arm type	Experimental

Investigational medicinal product name	Cell culture-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	cTIV, Optaflu
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

Arm title	Cohort 3 eTIV (3-8 Years)

Arm description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

Arm type	Active comparator
Investigational medicinal product name	Egg-derived trivalent influenza vaccine
Investigational medicinal product code	
Other name	eTIV, Fluvirin
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of one 0.5 mL dose for Cohorts 1 and 2 and two 0.5 mL doses administered four weeks apart for Cohort 3; all injections were administered IM in the deltoid muscle, preferably of the non-dominant arm.

Number of subjects in period 1	Cohort 1+2 cTIV (9-17 years)	Cohort 1+2 eTIV (9-17 years)	Cohort 3 cTIV (3-8 years)
Started	656	318	1608
Completed	643	312	1457
Not completed	13	6	151
Consent withdrawn by subject	2	1	19
Unable to classify	-	-	3
Adverse event	-	-	-
Inappropriate enrolment	-	-	4
Lost to follow-up	10	5	124
Protocol deviation	1	-	1

Number of subjects in period 1	Cohort 3 eTIV (3-8 Years)
Started	1022
Completed	919
Not completed	103
Consent withdrawn by subject	21
Unable to classify	4
Adverse event	2
Inappropriate enrolment	1
Lost to follow-up	75
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1+2 cTIV (9-17 years)
Reporting group description:	
All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.	
Reporting group title	Cohort 1+2 eTIV (9-17 years)
Reporting group description:	
All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.	
Reporting group title	Cohort 3 cTIV (3-8 years)
Reporting group description:	
All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.	
Reporting group title	Cohort 3 eTIV (3-8 Years)
Reporting group description:	
All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg -derived trivalent influenza vaccine.	

Reporting group values	Cohort 1+2 cTIV (9-17 years)	Cohort 1+2 eTIV (9-17 years)	Cohort 3 cTIV (3-8 years)
Number of subjects	656	318	1608
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	12.6	12.6	5.5
standard deviation	± 2.6	± 2.5	± 1.7
Gender categorical			
Units: Subjects			
Female	304	154	795
Male	352	164	813

Reporting group values	Cohort 3 eTIV (3-8 Years)	Total	
Number of subjects	1022	3604	
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	5.4		
standard deviation	± 1.7	-	
Gender categorical			
Units: Subjects			
Female	494	1747	
Male	528	1857	

End points

End points reporting groups

Reporting group title	Cohort 1+2 cTIV (9-17 years)
Reporting group description:	
All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.	
Reporting group title	Cohort 1+2 eTIV (9-17 years)
Reporting group description:	
All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.	
Reporting group title	Cohort 3 cTIV (3-8 years)
Reporting group description:	
All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.	
Reporting group title	Cohort 3 eTIV (3-8 Years)
Reporting group description:	
All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg -derived trivalent influenza vaccine.	
Subject analysis set title	cTIV- Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects with at least one vaccination and who provided some postvaccination safety data.	
Subject analysis set title	eTIV - Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects with at least one vaccination and who provided some postvaccination safety data.	
Subject analysis set title	Cohort 1 cTIV- (9-17 Years)- PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the Modified Intention To Treat (MITT) population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding.	
Subject analysis set title	Cohort 1 eTIV- (9-17 Years)- PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding.	
Subject analysis set title	cTIV - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding.	
Subject analysis set title	eTIV - PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the MITT population who received all doses of vaccine correctly, who provided evaluable serum samples at the relevant time points and who had no major protocol violations as defined prior to unblinding.	

Primary: 1) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in Post Vaccination Geometric Mean Titers

End point title	1) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in Post Vaccination Geometric Mean Titers[1]

End point description:

To demonstrate non-inferiority of the post vaccination hemagglutination inhibition (HI) geometric mean titer (GMT) of the cell culture-derived influenza (cTIV) vaccine to the corresponding GMT of the egg-derived (eTIV_f) influenza vaccine, for all three strains, after two injections administered four weeks apart to a subset of children 3-8 years of age.
GMTs were evaluated using two assays, HI egg derived antigen assay and HI cell derived antigen assay.
The analysis was performed on the per-protocol dataset

End point type	Primary

End point timeframe:

Day 50 post vaccination

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Titers				
geometric mean (confidence interval 95%)				
A/H1N1 (egg derived antigen assay)	407 (358 to 462)	477 (419 to 542)		
A/H3N2 (egg derived antigen assay)	768 (666 to 885)	1293 (1121 to 1491)		
B (egg derived antigen assay)	25 (21 to 29)	44 (38 to 51)		
A/H1N1 (cell derived antigen assay) (N=522,513)	563 (501 to 634)	610 (542 to 686)		
A/H3N2 (cell derived antigen assay) (N=522,513)	858 (744 to 990)	1329 (1152 to 1533)		
B (cell derived antigen assay) (N=522,513)	53 (46 to 62)	62 (53 to 72)		

Statistical analyses

Statistical analysis title	A/H1N1-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI egg-derived antigen assay

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.01

Notes:

[2] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Statistical analysis title	A/H3N2-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI egg-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.72

Notes:

[3] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Statistical analysis title	B-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against influenza B strain as measured by HI egg-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.68

Notes:

[4] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Statistical analysis title	A/H1N1-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.08

Notes:

[5] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Statistical analysis title	A/H3N1-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI cell-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.78

Notes:

[6] - Cell derived vaccine (cTIV) was considered non-inferior to egg-derived vaccine (eTIV) in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Statistical analysis title	B-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANOVA
Parameter estimate	Ratio of GMTs
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.06

Notes:

[7] - Cell derived vaccine was considered non-inferior to egg-derived vaccine in post vaccination HI GMTs if, for all three influenza strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (cTIV/eTIV) was >0.667.

Primary: 2) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in the Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Titers

End point title	2) Non-inferiority of the Cell Culture-derived Vaccine to the Egg-derived Vaccine in 3-8 Years Old Children in the Percentage of Subjects Achieving Seroconversion or Significant Increase in Antibody Titers[8]

End point description:

To demonstrate non-inferiority of the cell culture-derived influenza (cTIV) vaccine to the egg-derived (eTIV_f) influenza vaccine in the percentage of subjects achieving seroconversion or significant increase in antibody titer post vaccination, for all three strains, after two injections administered four weeks apart in children 3-8 years of age.
Seroconversion rate was evaluated using two assays- HI egg derived antigen assay and HI cell derived antigen assay.
The analysis was performed on the per-protocol dataset

End point type	Primary

End point timeframe:

Day 50 post vaccination

Notes:

[8] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Percentage				
number (confidence interval 95%)				
A/H1N1 (egg derived antigen assay)	94 (92 to 96)	96 (94 to 97)		
A/H3N2 (egg derived antigen assay)	77 (73 to 81)	86 (82 to 89)		
B (egg derived antigen assay)	38 (34 to 42)	53 (49 to 58)		
A/H1N1 (cell derived antigen assay) (N=522,513)	96 (93 to 97)	96 (94 to 98)		
A/H3N2 (cell derived antigen assay) (N=522,513)	80 (76 to 83)	85 (82 to 88)		
B (cell derived antigen assay) (N=522,513)	58 (54 to 63)	58 (54 to 63)		

Statistical analyses

Statistical analysis title	A/H1N1-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI egg-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)

Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Method	Binomial or Miettinen & Nurimen Method
Parameter estimate	Difference in % (cTIV minus eTIV)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	1

Notes:

[9] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Statistical analysis title	A/H3N2-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI egg-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Method	Binomial or Miettinen & Nurimen Method
Parameter estimate	Difference in % (cTIV minus eTIV):
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	-4

Notes:

[10] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Statistical analysis title	B-Egg derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against influenza B strain as measured by HI egg-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Method	Binomial or Miettinen & Nurimen method
Parameter estimate	Difference in % (cTIV minus eTIV):
Point estimate	-15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	-9

Notes:

[11] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Statistical analysis title	A/H1N1-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H1N1 influenza strain as measured by HI cell-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Method	Binominal or Miettinen &Nurimen method
Parameter estimate	Difference in % (cTIV minus eTIV
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2

Notes:

[12] - cTIV was considered non-inferior to eTIV in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Statistical analysis title	A/H3N2-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against A/H3N2 influenza strain as measured by HI cell-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)
Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Method	Binominal or Miettinen &Nurimen method
Parameter estimate	Difference in % (cTIV minus eTIV)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	0

Notes:

[13] - cTIV was considered non-inferior to eTIV_f in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Statistical analysis title	B-Cell derived antigen assay

Statistical analysis description:

Non-inferiority of cTIV to eTIV against B influenza strain as measured by HI cell-derived antigen assay.

Comparison groups	Cohort 3 cTIV (3-8 years) v Cohort 3 eTIV (3-8 Years)

Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Method	Binominal or Miettinen &Nurimen method
Parameter estimate	Difference in % (cTIV minus eTIV)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	6

Notes:

[14] - cTIV was considered non-inferior to eTIV_f in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (cTIV minus eTIV) was >-10%.

Secondary: 3) Geometric Mean Titers After 1 Dose of the Cell Culture-derived or the Egg- derived Influenza Vaccine in 9-17 Years Old Children and Adolescents

End point title	3) Geometric Mean Titers After 1 Dose of the Cell Culture-derived or the Egg- derived Influenza Vaccine in 9-17 Years Old Children and Adolescents

End point description:

To evaluate immunogenicity in terms of Geometric Mean Titers (GMTs) in children 9-17 years of age after one injection of either cTIV vaccine or eTIV_f.
GMTs were evaluated using two assays, HI egg derived antigen assay and HI cell derived antigen assay.
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 post vaccination

End point values	Cohort 1 cTIV-(9-17 Years)-PPS	Cohort 1 eTIV-(9-17 Years)-PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	144		
Units: Titers				
geometric mean (confidence interval 95%)				
Baseline (A/H1N1) egg derived antigen assay	55 (42 to 72)	78 (60 to 101)		
Day 29 (A/H1N1) egg derived antigen assay	879 (728 to 1062)	1107 (918 to 1334)		
Baseline (A/H3N2) egg derived antigen assay	121 (94 to 155)	151 (118 to 193)		
Day 29 (A/H3N2) egg derived antigen assay	706 (607 to 821)	1857 (1598 to 2157)		
Baseline (B) Egg derived antigen assay	9.65 (8.2 to 11)	9.92 (8.45 to 12)		
Day 29 (B) egg derived antigen assay	58 (48 to 71)	105 (86 to 129)		
Baseline(A/H1N1)Cell derived assay	70 (53 to 92)	90 (69 to 119)		
Day 29 (A/H1N1) cell derived antigen assay	1076 (886 to 1307)	1296 (1069 to 1571)		

Baseline(A/H3N2)cell derived assay(N=141,144)	125 (98 to 158)	144 (114 to 182)		
Day 29 (A/H3N2) cell derived antigen assay	676 (585 to 783)	1651 (1429 to 1908)		
Baseline(B)cell derived assay(N=141,144)	22 (18 to 27)	25 (21 to 30)		
Day 29 (B) cell derived antigen assay	136 (113 to 163)	186 (155 to 222)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4) Geometric Mean Ratio After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine in 9-17 Year-old Children and Adolescents.

End point title	4) Geometric Mean Ratio After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine in 9-17 Year-old Children and Adolescents.

End point description:

Immunogenicity was evaluated in terms of Geometric Mean Ratio (GMRs) in 9-17 year-old children and adolescents after one injection of either cTIV vaccine or eTIV.
The criterion is met according to European (CHMP) guideline if the mean geometric increase GMR (day29/day1) in HI antibody titer is >2.5.
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 post vaccination

End point values	Cohort 1 cTIV-(9-17 Years)-PPS	Cohort 1 eTIV-(9-17 Years)-PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	144		
Units: Ratio				
geometric mean (confidence interval 95%)				
Day 29 (A/H1N1)egg derived antigen assay	16 (12 to 21)	14 (11 to 19)		
Day 29 (A/H3N2) egg derived antigen assay	5.84 (4.43 to 7.7)	12 (9.33 to 16)		
Day 29 (B) egg derived antigen assay	6.03 (4.77 to 7.62)	11 (8.43 to 13)		
Day29(A/H1N1)cell derived antigen assay(N=141,144)	15 (12 to 21)	14 (11 to 19)		
Day29(A/H3N2)cell derived antigen assay(N=141,144)	5.45 (4.21 to 7.06)	11 (8.87 to 15)		
Day29(B) cell derived antigen assay(N=141,144)	6.15 (4.96 to 7.63)	7.37 (5.96 to 9.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5) Percentage of 9-17 Year-old Children and Adolescents Achieving HI Titers ≥40 After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

End point title	5) Percentage of 9-17 Year-old Children and Adolescents Achieving HI Titers ≥40 After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

End point description:

To evaluate immunogenicity in terms of percentage of 9-17 year-old children and adolescents achieving HI titers ≥40, after one injection of either the cTIV vaccine or the eTIV_f vaccine.
This criterion is met according to European (CHMP) guideline if the percentage of subjects achieving HI titers ≥40 is >70% and according to the US (CBER)guideline is met if the lower bound of the two sided 95%CI for percentage of subjects achieving HI titers ≥40 is ≥70%.
The analysis was performed on PPS

End point type	Secondary

End point timeframe:

Day 29 post vaccination

End point values	Cohort 1 cTIV-(9-17 Years)-PPS	Cohort 1 eTIV-(9-17 Years)-PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	144		
Units: Percentage				
number (confidence interval 95%)				
Prevaccination(A/H1N1)egg derived antigen assay	65 (57 to 73)	75 (67 to 82)		
Day 29 (A/H1N1) egg derived antigen assay	99 (96 to 100)	99 (95 to 100)		
Prevaccination(A/H3N2) egg derived antigen assay	82 (74 to 88)	86 (79 to 91)		
Day 29 (A/H3N2) egg derived antigen assay	100 (97 to 100)	100 (97 to 100)		
Prevaccination(B)egg derived antigen assay	17 (11 to 24)	13 (8 to 19)		
Day 29 (B) egg derived antigen assay	75 (67 to 82)	84 (77 to 90)		
Prevaccination(H1N1)cell derived assay(N=141,144)	67 (59 to 75)	78 (71 to 85)		
Day 29 (A/H1N1)cell derived antigen assay	99 (96 to 100)	98 (94 to 100)		
Prevaccination (H3N2)cell derived assay(N=141,144)	83 (76 to 89)	86 (79 to 91)		
Day 29 (A/H3N2) cell derived antigen assay	100 (97 to 100)	100 (97 to 100)		
Prevaccination (B) cell derived assay(N=141,144)	40 (32 to 49)	47 (38 to 55)		
Day 29 (B) cell derived antigen assay	95 (90 to 98)	94 (89 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6) Percentage of 9-17 Year-old Children and Adolescents With Seroconversion or Significant Increase After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

End point title	6) Percentage of 9-17 Year-old Children and Adolescents With Seroconversion or Significant Increase After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

End point description:

Seroconversion or significant increase as per CHMP criteria is defined as percentage of subjects with a pre vaccination HI titer <10 to a post vaccination titer ≥40 or a pre vaccination HI titer ≥10 and a ≥4-fold increase in post vaccination HI antibody titer.
According to the CHMP criteria, the percentage of subjects achieving seroconversion or significant increase should be >40%.
According to the CBER criteria, the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion/significant increase should be ≥40%.

End point type	Secondary

End point timeframe:

Day 29 post vaccination

End point values	Cohort 1 cTIV-(9-17 Years)-PPS	Cohort 1 eTIV-(9-17 Years)-PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	144		
Units: Percentage				
number (confidence interval 95%)				
Day 29 (A/H1N1) egg derived antigen assay	77 (70 to 84)	77 (69 to 84)		
Day 29 (A/H3N2) egg derived antigen assay	56 (48 to 65)	77 (69 to 84)		
Day 29 (B) egg derived antigen assay	56 (48 to 65)	71 (63 to 78)		
Day29(A/H1N1)cell derived antigen assay(N=141,144)	74 (66 to 81)	74 (66 to 81)		
Day29(A/H3N2)cell derived antigen assay(N=141,144)	52 (44 to 61)	78 (70 to 84)		
Day29(B)cell derived antigen assay (N=141,144)	63 (55 to 71)	69 (61 to 76)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7) Geometric Mean Titers After Two Doses of the Cell Derived or the Egg Derived Vaccine in 3-8 Year-old Children

End point title	7) Geometric Mean Titers After Two Doses of the Cell Derived or the Egg Derived Vaccine in 3-8 Year-old Children[15]

End point description:

To evaluate immunogenicity in terms of Geometric Mean Titers (GMTs) in children 3-8 years of age after two doses of either cTIV vaccine or eTIV, administered 4 weeks apart.
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

[15] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Titers				
geometric mean (confidence interval 95%)				
Baseline (A/H1N1) egg derived antigen assay	16 (14 to 18)	15 (13 to 17)		
Day29(A/H1N1)egg derived antigen assay(N=515,507)	152 (124 to 186)	157 (128 to 192)		
Day50(A/H1N1)egg derived antigen assay	407 (358 to 462)	477 (419 to 542)		
Baseline (A/H3N2) egg derived antigen assay	68 (58 to 80)	74 (63 to 87)		
Day29(A/H3N2)egg derived antigen assay(N=515,507)	584 (478 to 713)	1075 (880 to 1312)		
Day50(A/H3N2)egg derived antigen assay	768 (666 to 885)	1293 (1121 to 1491)		
Baseline (B) egg derived antigen assay	6.16 (5.86 to 6.48)	6.24 (5.93 to 6.56)		
Day29(B) egg derived antigen assay (N=515,507)	19 (16 to 22)	27 (23 to 33)		
Day 50 (B) egg derived antigen assay	25 (21 to 29)	44 (38 to 51)		
Baseline (A/H1N1) cell derived antigen assay	19 (16 to 22)	17 (14 to 19)		
Day 29 (A/H1N1) cell derived antigen assay	234 (194 to 283)	192 (159 to 232)		
Day50(A/H1N1)cell derived antigen assay(N=522,513)	563 (501 to 634)	610 (542 to 686)		
Baseline (A/H3N2) cell derived antigen assay	75 (64 to 88)	85 (72 to 99)		
Day 29 (A/H3N2) cell derived antigen assay	653 (536 to 795)	1099 (903 to 1339)		
Day50(A/H3N2)cell derived antigen assay(N=522,513)	858 (744 to 990)	1329 (1152 to 1533)		
Baseline (B) cell derived antigen assay	8.22 (7.59 to 8.9)	8.72 (8.05 to 9.45)		
Day 29 (B) cell derived antigen assay	29 (24 to 36)	36 (30 to 44)		
Day50 (B) cell derived antigen assay(N=522,513)	53 (46 to 62)	62 (53 to 72)		

Statistical analyses

No statistical analyses for this end point

Secondary: 8) Geometric Mean Ratio After Two Doses of the Cell-derived or the Egg-derived Vaccine in 3-8 Year-old Children

End point title	8) Geometric Mean Ratio After Two Doses of the Cell-derived or the Egg-derived Vaccine in 3-8 Year-old Children[16]

End point description:

To evaluate immunogenicity in terms of Geometric Mean Ratio (GMR) in children 3-8 years of age after two doses of either the cTIV vaccine or the eTIV vaccine, administered 4 weeks apart according to the CHMP criteria.
The criterion is met according to the European (CHMP) guideline if the mean geometric increase(GMR day 29/day 1 and GMR day 50/day 1) in HI antibody titer is >2.5
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

[16] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Ratios				
number (confidence interval 95%)				
Day29 (A/H1N1)egg derived antigen assay(N=515,507)	9.58 (8.37 to 11)	11 (9.36 to 12)		
Day 50 (A/H1N1) egg derived antigen assay	25 (23 to 28)	33 (29 to 36)		
Day29 (A/H3N2)egg derived antigen assay(N=515,507)	8.65 (7.4 to 10)	15 (13 to 17)		
Day 50 (A/H3N2) egg derived antigen assay	11 (9.84 to 13)	17 (15 to 20)		
Day 29 (B) egg derived assay (N=515,507)	3.04 (2.59 to 3.57)	4.36 (3.71 to 5.12)		
Day 50 (B) egg derived antigen assay	3.99 (3.49 to 4.57)	7.04 (6.15 to 8.07)		
Day 29 (A/H1N1) cell derived antigen assay	13 (11 to 14)	12 (10 to 13)		
Day50(A/H1N1)cell derived antigen assay(N=522,513)	30 (27 to 34)	37 (33 to 42)		
Day 29 (A/H3N2) cell derived antigen assay	8.73 (7.54 to 10)	13 (11 to 15)		
Day50(A/H3N2)cell derived antigen assay(N=522,513)	12 (10 to 13)	16 (14 to 18)		
Day 29 (B) cell derived antigen assay	3.59 (3.08 to 4.19)	4.14 (3.55 to 4.82)		
Day 50 (B) cell derived antigen assay(N=522,513)	6.5 (5.75 to 7.34)	7.06 (6.24 to 7.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9) Percentage of 3-8 Year-old Children Achieving HI Titers ≥ 40 After Two Doses of the Cell Culture Derived or the Egg Derived Influenza Vaccine.

End point title	9) Percentage of 3-8 Year-old Children Achieving HI Titers ≥ 40

	After Two Doses of the Cell Culture Derived or the Egg Derived Influenza Vaccine.[17]

End point description:

To evaluate immunogenicity in terms of HI titers ≥40, in children 3-8 years of age after two doses of either cTIV vaccine or eTIV_f vaccine, administered 4 weeks apart.
The criterion is met according to European (CHMP) guideline if the percentage of subjects achieving HI titers ≥40 is >70% and according to the US (CBER) guideline if the lower bound of the two sided 95%CI for percentage of subjects achieving HI titers ≥40 is ≥70%.
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

[17] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Percentage				
number (confidence interval 95%)				
Prevaccination (A/H1N1) egg derived antigen assay	35 (30 to 39)	31 (27 to 35)		
Day29(A/H1N1)egg derived antigen assay (N=515,507)	72 (68 to 76)	68 (64 to 72)		
Day 50 (A/H1N1) egg derived antigen assay	96 (94 to 98)	97 (95 to 98)		
Prevaccination (A/H3N2) egg derived antigen assay	67 (62 to 71)	70 (66 to 74)		
Day29(A/H3N2)egg derived antigen assay(N=515,507)	87 (84 to 90)	85 (82 to 88)		
Day50 (A/H3N2) egg derived antigen assay	96 (94 to 98)	94 (91 to 96)		
Prevaccination (B) egg derived antigen assay	4 (3 to 7)	4 (3 to 6)		
Day 29 (B) egg derived antigen assay (N=515,507)	35 (30 to 39)	40 (36 to 45)		
Day 50 (B) egg derived antigen assay	40 (35 to 44)	55 (51 to 95)		
Prevaccination (A/H1N1) cell derived antigen assay	36 (32 to 40)	33 (29 to 38)		
Day 29 (A/H1N1) cell derived antigen assay	82 (78 to 85)	76 (72 to 80)		
Day50(A/H1N1)cell derived antigen assay(N=522,513)	98 (97 to 99)	98 (96 to 99)		
Prevaccination (A/H3N2) cell derived antigen assay	71 (67 to 75)	75 (71 to 79)		
Day 29 (A/H3N2) cell derived antigen assay	89 (86 to 92)	85 (82 to 88)		
Day50(A/H3N2)cell derived antigen assay(N=522,513)	98 (96 to 99)	93 (91 to 95)		
Prevaccination (B) cell derived antigen assay	11 (8 to 14)	12 (10 to 16)		
Day 29 (B) cell derived antigen assay	43 (39 to 47)	45 (40 to 49)		
Day 50 (B) cell derived antigen assay (N=522,513)	60 (56 to 65)	62 (57 to 66)		

Statistical analyses

No statistical analyses for this end point

Secondary: 10) Percentage of 3-8 Year-old Children Achieving Seroconversion or Significant Increase in HI Titers After Two Doses of the Cell Culture-derived or the Egg-derived Influenza Vaccine.

End point title	10) Percentage of 3-8 Year-old Children Achieving Seroconversion or Significant Increase in HI Titers After Two Doses of the Cell Culture-derived or the Egg-derived Influenza Vaccine.[18]

End point description:

Seroconversion or significant increase as per CHMP criteria is defined as percentage of subjects with a pre vaccination HI titer <10 to a post vaccination titer ≥40 or a prevaccination HI titer ≥10 and a ≥4-fold increase in post vaccination HI antibody titer.
According to the CHMP criteria, the percentage of subjects achieving seroconversion or significant increase should be >40%.
According to the CBER criteria, the lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion/significant increase should be ≥40%.
The analysis was performed on the per-protocol dataset.

End point type	Secondary

End point timeframe:

Day 29 and Day 50 post vaccination

Notes:

[18] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	524	513		
Units: Percentage				
number (confidence interval 95%)				
Day29(A/H1N1) egg derived antigen assay(N=515,507)	70 (66 to 74)	67 (63 to 72)		
Day 50 (H1N1) egg derived antigen assay	94 (92 to 96)	96 (94 to 97)		
Day29(A/H3N2) egg derived antigen assay(N=515,507)	65 (61 to 70)	78 (74 to 81)		
Day 50 (A/H3N2) egg derived antigen assay	77 (73 to 81)	86 (82 to 89)		
Day29(B) egg derived antigen assay(N=515,507)	33 (29 to 37)	38 (34 to 43)		
Day 50 (B) egg derived antigen assay	38 (34 to 42)	53 (49 to 58)		
Day 29 (A/H1N1) cell derived antigen assay	79 (75 to 83)	75 (70 to 78)		
Day50(A/H1N1)cell derived antigen assay(N=522,513)	96 (93 to 97)	96 (94 to 98)		
Day 29 (A/H3N2) cell derived antigen assay	70 (66 to 74)	76 (72 to 80)		

Day50(A/H3N2)cell derived antigen assay(N=522,513)	80 (76 to 83)	85 (82 to 88)		
Day 29 (B) cell derived antigen assay	40 (36 to 44)	41 (37 to 45)		
Day 50(B)cell derived antigen assay(N=522,513)	58 (54 to 63)	58 (54 to 63)		

Statistical analyses

No statistical analyses for this end point

Secondary: 11) Number of 9-17 Year-old Children and Adolescents Reporting Local and Systemic Reactions After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine

End point title	11) Number of 9-17 Year-old Children and Adolescents Reporting Local and Systemic Reactions After 1 Dose of the Cell Culture-derived or the Egg-derived Influenza Vaccine[19]

End point description:

To evaluate safety and tolerability in terms of number of 9-17 year-old children and adolescents (cohorts 1 and 2)reporting local and systemic reactions following of one injection of the cTIV or the eTIV vaccine .

End point type	Secondary

End point timeframe:

Up to 7 days after vaccination

Notes:

[19] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 1+2 cTIV (9-17 years)	Cohort 1+2 eTIV (9-17 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	652	316		
Units: Participants				
Any Local	276	141		
Injection site pain	220	120		
Injection site erythema	91	45		
Injection site induration	44	28		
Injection site ecchymosis	34	10		
Injection site swelling	32	17		
Any Systemic	188	95		
Chills	26	13		
Malaise	60	34		
Myalgia	99	59		
Arthralgia	27	17		
Headache	92	44		
Sweating	14	3		
Fatigue	57	41		
Fever (≥38C) (N=651,316)	5	3		
Any Other	44	37		
Stayed at home (N=649,316)	9	10		
Analgesic Medication Used	42	31		

Statistical analyses

No statistical analyses for this end point

Secondary: 12) Number of 3-8 Year-old Children Reporting Local and Systemic Reactions After One and Two Doses of the Cell Culture-derived or Egg-derived Influenza Vaccine.

End point title	12) Number of 3-8 Year-old Children Reporting Local and Systemic Reactions After One and Two Doses of the Cell Culture-derived or Egg-derived Influenza Vaccine.[20]

End point description:

To evaluate the safety and tolerability of the cTIV and the eTIV_f influenza vaccines in 3-8 year-old children terms of number of participants reporting local and systemic reactions after each vaccination.

End point type	Secondary

End point timeframe:

Up to 7 days after each vaccination

Notes:

[20] - 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: There were no statistical analysis done to this endpoint.

End point values	Cohort 3 cTIV (3-8 years)	Cohort 3 eTIV (3-8 Years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1599	1013		
Units: Participants				
number (not applicable)				
Injection site pain	653	398		
Injection site erythema	337	206		
Injection site induration	141	84		
Injection site ecchymosis	144	99		
Injection site swelling	119	85		
Chills	70	68		
Malaise	156	117		
Myalgia	202	119		
Arthralgia	65	28		
Headache	182	144		
Sweating	47	28		
Fatigue	210	170		
Fever (≥ 38C)	75	60		
Oral temp; 38 to <38.9 C (N=1598,1013)	48	43		
Oral temp; 39 to < 40 C (N=1598,1013)	16	15		
Oral temp; ≥ 40 C (N=1598,1013)	6	1		
Stayed at home (N=1586, 1004))	77	63		
Analgesic Medication Used	221	148		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period (Day 1-181 for Cohorts 1 and 2, and Day 1-209 for cohort 3)

Adverse event reporting additional description:

Solicited AEs - day 1 through day 7 after vaccination.
All AEs- day 1 through day 29 (cohort 1&2); day 1 through day 50 (cohort 3).
SAEs, onset of chronic illness, and AEs that lead to withdrawal from the study and associated concomitant medications-day 29 to day 181 (cohort 1&2); day 50 through day 209 (cohort 3)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Cohort 1 & 2 cTIV (9-17 years)

Reporting group description:

All subjects aged 9-17 years received one 0.5 mL IM injection, of Cell Culture-derived trivalent influenza vaccine.

Reporting group title	Cohort 1 & 2 eTIV (9-17 years)

Reporting group description:

All subjects aged 9-17 years received one 0.5 mL injection, of egg -derived trivalent influenza vaccine.

Reporting group title	Cohort 3 cTIV(3-8 years)-First vaccination

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

Reporting group title	Cohort 3 eTIV(3-8 years)-First vaccination

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

Reporting group title	Cohort 3 cTIV(3-8 years)-Second vaccination

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart, of Cell Culture-derived trivalent influenza vaccine.

Reporting group title	Cohort 3 eTIV(3-8 years)-Second vaccination

Reporting group description:

All subjects aged 3-8 years received two 0.5 mL injections, administered four weeks apart of egg - derived trivalent influenza vaccine.

Serious adverse events	Cohort 1 & 2 cTIV (9-17 years)	Cohort 1 & 2 eTIV (9-17 years)	Cohort 3 cTIV(3-8 years)-First vaccination
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 652 (0.77%)	3 / 316 (0.95%)	2 / 1599 (0.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Body height below normal			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Injury, poisoning and procedural complications			
Concussion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	1 / 1599 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Thalassaemia beta			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Tonsillectomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Post procedural haemorrhage			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Appendix disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Reproductive system and breast disorders			
Ovarian torsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	1 / 316 (0.32%)	0 / 1599 (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			
Bronchitis chronic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Major depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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

Infections and infestations			
Abscess limb			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	1 / 1599 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	1 / 316 (0.32%)	0 / 1599 (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
Otitis media chronic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Pharyngotonsillitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	1 / 316 (0.32%)	0 / 1599 (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 tract infection viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 652 (0.00%)	1 / 316 (0.32%)	0 / 1599 (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
Viral infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 652 (0.15%)	0 / 316 (0.00%)	0 / 1599 (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
Diabetes mellitus			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 652 (0.00%)	0 / 316 (0.00%)	0 / 1599 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 3 eTIV(3-8 years)-First vaccination	Cohort 3 cTIV(3-8 years)-Second vaccination	Cohort 3 eTIV(3-8 years)-Second vaccination
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1013 (0.00%)	7 / 1557 (0.45%)	5 / 977 (0.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Body height below normal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Concussion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	2 / 1557 (0.13%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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
Eye injury			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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
Congenital, familial and genetic disorders			
Thalassaemia beta			
alternative assessment type: Non-			

systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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
Surgical and medical procedures			
Tonsillectomy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	1 / 977 (0.10%)
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			
Post procedural haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	1 / 977 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendix disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian torsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Bronchitis chronic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	1 / 977 (0.10%)
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			
Major depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	1 / 977 (0.10%)
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			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	1 / 977 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	1 / 977 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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
Pneumonia bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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
Streptococcal bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	0 / 1557 (0.00%)	0 / 977 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1013 (0.00%)	1 / 1557 (0.06%)	0 / 977 (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

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

Non-serious adverse events	Cohort 1 & 2 cTIV (9-17 years)	Cohort 1 & 2 eTIV (9-17 years)	Cohort 3 cTIV(3-8 years)-First vaccination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	328 / 652 (50.31%)	168 / 316 (53.16%)	799 / 1599 (49.97%)
Nervous system disorders			
Headache			
subjects affected / exposed	99 / 652 (15.18%)	47 / 316 (14.87%)	143 / 1599 (8.94%)
occurrences (all)	125	56	167
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	57 / 652 (8.74%)	41 / 316 (12.97%)	155 / 1599 (9.69%)
occurrences (all)	67	47	171
Injection site erythema			
subjects affected / exposed	91 / 652 (13.96%)	45 / 316 (14.24%)	197 / 1599 (12.32%)
occurrences (all)	94	45	198
Injection site haemorrhage			

subjects affected / exposed	34 / 652 (5.21%)	10 / 316 (3.16%)	98 / 1599 (6.13%)
occurrences (all)	37	11	106
Injection site induration			
subjects affected / exposed	44 / 652 (6.75%)	28 / 316 (8.86%)	87 / 1599 (5.44%)
occurrences (all)	44	29	89
Injection site pain			
subjects affected / exposed	220 / 652 (33.74%)	120 / 316 (37.97%)	451 / 1599 (28.21%)
occurrences (all)	227	122	462
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	60 / 652 (9.20%)	34 / 316 (10.76%)	103 / 1599 (6.44%)
occurrences (all)	68	41	118
Pyrexia			
subjects affected / exposed	12 / 652 (1.84%)	5 / 316 (1.58%)	88 / 1599 (5.50%)
occurrences (all)	13	7	96
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 652 (1.53%)	4 / 316 (1.27%)	124 / 1599 (7.75%)
occurrences (all)	10	4	130
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	99 / 652 (15.18%)	59 / 316 (18.67%)	141 / 1599 (8.82%)
occurrences (all)	107	67	150

Non-serious adverse events	Cohort 3 eTIV(3-8 years)-First vaccination	Cohort 3 cTIV(3-8 years)-Second vaccination	Cohort 3 eTIV(3-8 years)-Second vaccination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	507 / 1013 (50.05%)	670 / 1557 (43.03%)	413 / 977 (42.27%)
Nervous system disorders			
Headache			
subjects affected / exposed	111 / 1013 (10.96%)	94 / 1557 (6.04%)	73 / 977 (7.47%)
occurrences (all)	135	110	89
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	119 / 1013 (11.75%)	99 / 1557 (6.36%)	82 / 977 (8.39%)
occurrences (all)	143	110	92
Injection site erythema			
subjects affected / exposed	138 / 1013 (13.62%)	209 / 1557 (13.42%)	118 / 977 (12.08%)
occurrences (all)	139	211	121
Injection site haemorrhage			
subjects affected / exposed	60 / 1013 (5.92%)	52 / 1557 (3.34%)	43 / 977 (4.40%)
occurrences (all)	67	58	51
Injection site induration			
subjects affected / exposed	44 / 1013 (4.34%)	66 / 1557 (4.24%)	51 / 977 (5.22%)
occurrences (all)	45	66	51
Injection site pain			
subjects affected / exposed	251 / 1013 (24.78%)	421 / 1557 (27.04%)	266 / 977 (27.23%)
occurrences (all)	261	430	278
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	78 / 1013 (7.70%)	76 / 1557 (4.88%)	50 / 977 (5.12%)
occurrences (all)	85	86	56
Pyrexia			
subjects affected / exposed	73 / 1013 (7.21%)	63 / 1557 (4.05%)	44 / 977 (4.50%)
occurrences (all)	84	70	49
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	75 / 1013 (7.40%)	70 / 1557 (4.50%)	51 / 977 (5.22%)
occurrences (all)	87	75	52
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	76 / 1013 (7.50%)	100 / 1557 (6.42%)	67 / 977 (6.86%)
occurrences (all)	88	28	22

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22301476