Clinical trial results:
A Multi-center, Phase III, Randomized, Observer Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Trivalent Subunit Inactivated Influenza Vaccine (Agriflu™) in Healthy Children and Adolescents 3 to 17 Years of Age.

Summary

EudraCT number	2014-004498-17
Trial protocol	Outside EU/EEA
Global end of trial date	29 September 2011

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	06 March 2015
Version creation reason	• Correction of full data set Required for the re-QC because of EudraCT system glitch as possible updates to results are required. Moreover, the study is now transferred to another primary user.

Trial information

Trial identification

Sponsor protocol code	V71_18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01209780
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics, Inc
Sponsor organisation address	Via Fiorentina 1, Siena, Italy, 53100
Public contact	Novartis Vaccines and Diagnostics, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Novartis Vaccines and Diagnostics, 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	07 February 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of the HI antibody responses of Agriflu for the three influenza strains when compared to US licensed trivalent inactivated influenza vaccines (controls) 21 days after last vaccination in children ages 3 to 8 years as measured by:
▫differences in percentage of subjects achieving seroconversion
▫ vaccines ratio of post-vaccination geometric mean titers (GMT)

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practices (GCPs) and the applicable regulatory requirement (s) for the country in which the trial was conducted, Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs).

Background therapy:

Not Applicable

Evidence for comparator:

Not Applicable

Actual start date of recruitment	30 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Panama: 77
Country: Number of subjects enrolled	Philippines: 2092
Country: Number of subjects enrolled	Colombia: 635
Worldwide total number of subjects	2804
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	2060
Adolescents (12-17 years)	744
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 13 centers across 4 countries: Mexico, Colombia, Panama and Philippines.

Pre-assignment

Screening details:

Subjects in each age group were randomly assigned (2:1) to receive either Agriflu (thimerosal-free formulation) or Fluvirin (as comparator for 4 to 17 years) or Fluzone (as comparator for children 3 to 4 years, since Fluvirin is not approved below 4 years of age).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TIV (3-8Yrs)

Arm description:

The group consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). The non-naive subjects received one dose and naive subjects received two doses of investigational Trivalent Inactivated Influenza Vaccine (TIV).

Arm type	Experimental
Investigational medicinal product name	Trivalent Subunit Inactivated Influenza Vaccine (TIV)
Investigational medicinal product code	
Other name	Agrippal
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose 0.5 mL of injectable solution was administered intramuscularly.

Arm title	Control (3-8 Yrs)

Arm description:

The group [control (4-8 years) + control (3-<4 years)] consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). Subjects (4-<9 years) received Trivalent Inactivated Subunit Influenza Vaccine (TIVf) and subjects (3-<4 years) received comparator TIV. The non-naive subjects received one dose and naive subjects received two doses of control vaccine.

Arm type	Active comparator
Investigational medicinal product name	Trivalent Inactivated Subunit Influenza Vaccine (TIV)
Investigational medicinal product code	
Other name	Fluzone
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose 0.5 mL of injectable solution was administered intramuscularly.

Investigational medicinal product name	Trivalent Inactivated Subunit Influenza Vaccine (TIVf)
Investigational medicinal product code	
Other name	Fluvirin
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose 0.5 mL of injectable solution was administered intramuscularly.

Arm title	TIV (9-17 Yrs)

Arm description:

All subjects in this group were non-naive and received one dose of investigational TIV.

Arm type	Experimental
Investigational medicinal product name	Trivalent Subunit Inactivated Influenza Vaccine (TIV)
Investigational medicinal product code	
Other name	Agrippal
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose 0.5 mL of injectable solution was administered intramuscularly.

Arm title	Control (9-17 yrs)

Arm description:

All subjects in this group were non-naive and received one dose of US licensed control vaccine TIVf.

Arm type	Active comparator
Investigational medicinal product name	Trivalent Inactivated Subunit Influenza Vaccine(TIVf)
Investigational medicinal product code	
Other name	Fluvirin
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each dose 0.5 mL of injectable solution was administered intramuscularly.

Number of subjects in period 1	TIV (3-8Yrs)	Control (3-8 Yrs)	TIV (9-17 Yrs)
Started	1042	533	817
Completed	1016	511	807
Not completed	26	22	10
Consent withdrawn by subject	9	3	1
Adverse Event	-	1	-
Inappropriate enrollment	-	2	-
Lost to follow-up	17	15	9
Protocol deviation	-	1	-

Number of subjects in period 1	Control (9-17 yrs)
Started	412
Completed	407
Not completed	5

Consent withdrawn by subject	-
Adverse Event	-
Inappropriate enrollment	1
Lost to follow-up	4
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	TIV (3-8Yrs)

Reporting group description:

The group consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). The non-naive subjects received one dose and naive subjects received two doses of investigational Trivalent Inactivated Influenza Vaccine (TIV).

Reporting group title	Control (3-8 Yrs)

Reporting group description:

The group [control (4-8 years) + control (3-<4 years)] consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). Subjects (4-<9 years) received Trivalent Inactivated Subunit Influenza Vaccine (TIVf) and subjects (3-<4 years) received comparator TIV. The non-naive subjects received one dose and naive subjects received two doses of control vaccine.

Reporting group title	TIV (9-17 Yrs)

Reporting group description:

All subjects in this group were non-naive and received one dose of investigational TIV.

Reporting group title	Control (9-17 yrs)

Reporting group description:

All subjects in this group were non-naive and received one dose of US licensed control vaccine TIVf.

Reporting group values	TIV (3-8Yrs)	Control (3-8 Yrs)	TIV (9-17 Yrs)
Number of subjects	1042	533	817
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	1042	533	314
Adolescents (12-17 years)	0	0	503
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	5.6	5.6	12.4
standard deviation	± 1.6	± 1.6	± 2.4
Gender categorical Units: Subjects			
Female	517	269	398
Male	525	264	419

Reporting group values	Control (9-17 yrs)	Total	
Number of subjects	412	2804	

Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	171	2060	
Adolescents (12-17 years)	241	744	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	12.3		
standard deviation	± 2.3	-	
Gender categorical Units: Subjects			
Female	215	1399	
Male	197	1405	

End points

End points reporting groups

Reporting group title	TIV (3-8Yrs)

Reporting group description:

The group consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). The non-naive subjects received one dose and naive subjects received two doses of investigational Trivalent Inactivated Influenza Vaccine (TIV).

Reporting group title	Control (3-8 Yrs)

Reporting group description:

The group [control (4-8 years) + control (3-<4 years)] consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). Subjects (4-<9 years) received Trivalent Inactivated Subunit Influenza Vaccine (TIVf) and subjects (3-<4 years) received comparator TIV. The non-naive subjects received one dose and naive subjects received two doses of control vaccine.

Reporting group title	TIV (9-17 Yrs)

Reporting group description:

All subjects in this group were non-naive and received one dose of investigational TIV.

Reporting group title	Control (9-17 yrs)

Reporting group description:

All subjects in this group were non-naive and received one dose of US licensed control vaccine TIVf.

Subject analysis set title	All Enrolled Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects who have been enrolled.

Subject analysis set title	Immunogenicity Per Protocol (PP) Population
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the Full Analysis Set/MITT population who:
▫ correctly received all study vaccinations
▫ provided evaluable serum samples at the relevant time points, and
▫ had no major protocol violation as defined prior to unblinding
A major violation is defined (prior to analysis) as a protocol deviation that was considered to have a significant impact on the immunogenicity result of the subject.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the Exposed population who provided post vaccination safety data.

Subject analysis set title	Control (3-8 Years)
Subject analysis set type	Per protocol

Subject analysis set description:

The group [control (4-8 years) + control (3 to<4 years)] consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination).Subjects (4-<9 years) received TIVf and subjects (3-<4 years) received comparator TIV. The non-naive subjects received one dose and naive subjects received two doses of vaccine.

All subjects in the Full Analysis Set/MITT population who:
▫ correctly received all study vaccinations
▫ provided evaluable serum samples at the relevant time points, and
▫ had no major protocol violation as defined prior to unblinding
A major violation is defined (prior to analysis) as a protocol deviation that was considered to have a significant impact on the immunogenicity result of the subject.

Subject analysis set title	Control (3 to < 4Years)

Subject analysis set type	Per protocol

Subject analysis set description:

The group consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination. The non-naive subjects received one dose and non-naive subjects received two doses of US licensed control vaccine- comparator TIV.

Primary: Comparison of Antibody Responses of Investigational TIV to Control Vaccine in Terms of the Percentage of Subjects Achieving Seroconversion.

End point title	Comparison of Antibody Responses of Investigational TIV to Control Vaccine in Terms of the Percentage of Subjects Achieving Seroconversion.[1]

End point description:

The non-inferiority of the antibody responses of investigational TIV compared to control TIV assessed in terms of the percentage of subjects achieving seroconversion, against the three homologous vaccine strains, in children 3 to 8 years of age, at 21 days after last vaccination.
Seroconversion was defined as a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40 or as a pre-vaccination HI titer ≥1:10 and at minimum four-fold rise in post-vaccination antibody titer.
Analysis was done on per protocol population.

End point type	Primary

End point timeframe:

Day 22 for non-naive/Day 50 for naive subjects

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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	468		
Units: Percentage of Subjects				
number (confidence interval 95%)				
H1N1 strain (N=916,467)	95 (93 to 96)	94 (91 to 96)		
H3N2 strain (N=917,468)	78 (75 to 80)	87 (84 to 90)		
B strain	87 (84 to 89)	85 (82 to 89)		

Statistical analyses

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs): A/H1N1

Statistical analysis description:

Non-inferiority of investigational TIV to control TIV against A/H1N1 influenza strain considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	TIV (3-8Yrs) v Control (3-8 Yrs)
Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	Chi-squared
Parameter estimate	Control minus TIV
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	2

Notes:

[2] - Investigational TIV was to be considered non-inferior to the control TIV if two-sided 95% CI on the difference between the seroconversion rates, at 21 days after last vaccination, does not exceed 10% points assuming that the true unknown rates of subjects with seroconversion for A/H1N1, A/H3N2 & B after 1 or 2 doses of TIV would be in the range of 83.5% to 74% & for comparator would be in the range of 85.5% to 71.5% using one-sided testing with an α = 0.025, power was estimated to be 92.5%.

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs): A/H3N2

Statistical analysis description:

Non-inferiority of investigational TIV to the control TIV against A/H3N2 strain considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	TIV (3-8Yrs) v Control (3-8 Yrs)
Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	Chi-squared
Parameter estimate	Control minus TIV
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	14

Notes:

[3] - Investigational TIV was to be considered non-inferior to the control TIV if two-sided 95% CI on the difference between the seroconversion rates, at 21 days after last vaccination, does not exceed 10% points assuming that the true unknown rates of subjects with seroconversion for A/H1N1, A/H3N2 & B after 1 or 2 doses of TIV would be in the range of 83.5% to 74% & for comparator would be in the range of 85.5% to 71.5% using one-sided testing with an α = 0.025, power was estimated to be 92.5%.

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs):B Strain

Statistical analysis description:

Non-inferiority of investigational TIV to the control TIV against B influenza strain considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	TIV (3-8Yrs) v Control (3-8 Yrs)
Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	Chi-squared
Parameter estimate	Control minus TIV
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	3

Notes:

[4] - Investigational TIV was to be considered non-inferior to the control TIV if two-sided 95% CI on the difference between the seroconversion rates, at 21 days after last vaccination, does not exceed 10% points assuming that the true unknown rates of subjects with seroconversion for A/H1N1, A/H3N2 & B after 1 or 2 doses of TIV would be in the range of 83.5% to 74% & for comparator would be in the range of 85.5% to 71.5% using one-sided testing with an α = 0.025, power was estimated to be 92.5%.

Primary: Comparison of Antibody Responses of Investigational TIV to Control Vaccine in Terms of Post Vaccination Geometric Mean Titers (GMTs)

End point title	Comparison of Antibody Responses of Investigational TIV to Control Vaccine in Terms of Post Vaccination Geometric Mean Titers (GMTs)[5]

End point description:

The non-inferiority of the antibody responses of investigational TIV compared to control vaccine assessed in terms of post vaccination GMTs, at 21 days after last vaccination against the three homologous vaccine strains in children aged 3 to 8 years.
Analysis was performed on the per protocol population.

End point type	Primary

End point timeframe:

Day 22 for non-naive/Day 50 for naive subjects

Notes:

[5] - 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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	468		
Units: Titers				
geometric mean (confidence interval 95%)				
Baseline (H1N1 strain, N=917,467)	26 (22 to 31)	28 (25 to 31)		
Day 22 or Day 50 (H1N1 strain, N=917,468)	1157 (1052 to 1272)	1501 (1283 to 1756)		
Baseline (H3N2 strain)	142 (127 to 158)	150 (129 to 175)		
Day 22 or Day 50 (H3N2 strain, N=917,468)	1385 (1300 to 1475)	2032 (1843 to 2240)		
Baseline (B strain)	12 (11 to 13)	13 (12 to 14)		
Day 22 or Day 50 (B strain)	208 (193 to 224)	195 (174 to 217)		

Statistical analyses

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs): A/H1N1 Strain

Statistical analysis description:

Non-inferiority of investigational TIV to licensed control TIV against A/H1N1 influenza strain considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	TIV (3-8Yrs) v Control (3-8 Yrs)

Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	ANOVA
Parameter estimate	Ratio of GMTs Control:TIV
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	1.56

Notes:

[6] - Investigational TIV was to be considered non-inferior to control TIV, if for all three strains, the upper bound of the two-sided 95% CI on the ratio of the GMTs at 21 days after last vaccination does not exceed 1.5. Assuming standard deviation (SD) for the log transformed titer for strains A/H1N1, A/H3N2 & B at 21 days after 1 or 2 doses of TIV/comparator was in range of 0.91 to 0.65,the power for one-sided testing with an α = 0.025 was estimated to be 88.45% for non-inferiority GMT ratio.

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs): A/H3N2 Strain

Statistical analysis description:

Non-inferiority of investigational TIV to licensed control TIV against A/H3N2 influenza strain considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	TIV (3-8Yrs) v Control (3-8 Yrs)
Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANOVA
Parameter estimate	Ratio of GMTs Control: TIV
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.34
upper limit	1.64

Notes:

[7] - Investigational TIV was to be considered non-inferior to control TIV, if for all three strains, the upper bound of the two-sided 95% CI on the ratio of the GMTs at 21 days after last vaccination does not exceed 1.5. Assuming standard deviation (SD) for the log transformed titer for strains A/H1N1, A/H3N2 & B at 21 days after 1 or 2 doses of TIV/comparator was in range of 0.91 to 0.65,the power for one-sided testing with an α = 0.025 was estimated to be 88.45% for non-inferiority GMT ratio.

Statistical analysis title	TIV(3-8 Yrs) vs Control(3-8 Yrs): B Strain

Statistical analysis description:

Non-inferiority of investigational TIV to licensed control TIV against B influenza strain. Considering the two non-inferiority immunogenicity end-points for three influenza strains, a sample size of 1500 subjects (1000 in TIV and 500 in comparator) with a vaccine ratio of 2:1 was sufficient to reject the null hypotheses for the primary objective with a power of 81.82%.

Comparison groups	Control (3-8 Yrs) v TIV (3-8Yrs)

Number of subjects included in analysis	1386
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Ratio of GMTs Control: TIV
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.07

Notes:

[8] - Investigational TIV was to be considered non-inferior to control TIV, if for all three strains, the upper bound of the two-sided 95% CI on the ratio of the GMTs at 21 days after last vaccination does not exceed 1.5. Assuming standard deviation (SD) for the log transformed titer for strains A/H1N1, A/H3N2 & B at 21 days after 1 or 2 doses of TIV/comparator was in range of 0.91 to 0.65,the power for one-sided testing with an α = 0.025 was estimated to be 88.45% for non-inferiority GMT ratio.

Secondary: Percentages of Subjects Achieving HI Titers ≥40 Following Vaccination With Investigational TIV or Control Vaccine.

End point title	Percentages of Subjects Achieving HI Titers ≥40 Following Vaccination With Investigational TIV or Control Vaccine.[9]

End point description:

The percentages of 3 to 8 year old subjects achieving HI titers ≥40 after receiving either one or two doses of investigational TIV or control vaccine, 21 days after last vaccination, are reported.
This criterion 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%.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

Day 22 for non-naive/Day 50 for naive 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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	468		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Baseline (H1N1strain, N=917,467)	49 (46 to 53)	48 (44 to 53)		
Day 22 or Day 50 (H1N1 strain, N=917,468)	97 (95 to 98)	95 (93 to 97)		
Baseline (H3N2 strain)	84 (81 to 86)	85 (82 to 88)		
Day 22 or Day 50 (H3N2 strain, N=917,468)	100 (100 to 100)	100 (99 to 100)		
Baseline (B strain)	23 (21 to 26)	26 (22 to 30)		
Day 22 or Day 50 (B strain)	95 (93 to 96)	92 (90 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects With Seroconversion in Antibody Titers Following Vaccination With Investigational TIV or Control Vaccine.

End point title	Percentages of Subjects With Seroconversion in Antibody Titers Following Vaccination With Investigational TIV or Control Vaccine.[10]

End point description:

The percentages of 3 to 8 years-old subjects achieving seroconversion in HI antibody titers after receiving either one or two doses of investigational TIV or control vaccine, at 21 days after last vaccination, are reported.
This criterion, according to the US (CBER) guideline, is met if the lower limit of 95% CI of percentage of subjects achieving seroconversion or significant increase at day 22 and day 50 (21 days after last vaccination) is ≥40.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

Day 22 for non-naive/Day 50 for naive 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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	468		
Units: Percentages of Subjects				
number (confidence interval 95%)				
H1N1 strain (N= 916,467)	95 (93 to 96)	94 (91 to 96)		
H3N2 strain (N= 917,468)	78 (75 to 80)	87 (84 to 90)		
B strain	87 (84 to 89)	85 (82 to 89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Vaccine-naive Children Achieving HI Titers ≥40 After Receiving Two Doses of Investigational TIV or Control Vaccine.

End point title	Percentages of Vaccine-naive Children Achieving HI Titers ≥40 After Receiving Two Doses of Investigational TIV or Control Vaccine.[11]

End point description:

The percentage of 3 to 8 years-old vaccine-naive subjects achieving HI titers ≥40, after receiving two doses of investigational TIV or control vaccine. The time frame of evaluation was 28 days after first (Day 29) and 21 days after second vaccine dose (Day 50).
This criterion 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%, for each vaccine strain.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

Day 29 and Day 50

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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	820	413		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Day 1 (H1N1 strain, N=819,412)	49 (46 to 53)	48 (43 to 53)		
Day 29(H1N1 strain, N=819,413)	83 (80 to 86)	82 (78 to 86)		
Day 50 (H1N1 strain, N= 819,413)	99 (98 to 100)	98 (96 to 99)		
Day 1 (H3N2 strain)	88 (85 to 90)	90 (87 to 93)		
Day 29 (H3N2 strain, N= 819, 413)	99 (98 to 100)	98 (96 to 99)		
Day 50 (H3N2 strain, N= 819, 413)	100 (100 to 100)	100 (99 to 100)		
Day 1(B strain)	25 (22 to 28)	26 (22 to 31)		
Day 29(B strain, N= 820,412)	82 (79 to 84)	81 (77 to 85)		
Day 50 (B strain)	98 (96 to 99)	94 (92 to 96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Vaccine-naive Children Achieving Seroconversion in Antibody Titers, After Receiving Two Doses of Investigational TIV or Control Vaccine

End point title	Percentages of Vaccine-naive Children Achieving Seroconversion in Antibody Titers, After Receiving Two Doses of Investigational TIV or Control Vaccine[12]

End point description:

The percentages of 3 to 8 years-old vaccine naive children achieving seroconversion or significant increase in HI antibody titers after receiving two doses of investigational TIV or control vaccine, are reported. The time frame of evaluation was 28 days after first (Day 29) and 21 days after the second dose (Day 50).
This criterion, according to the US (CBER) guideline, is met if the lower limit of 95% CI of percentage of subjects achieving seroconversion or significant increase at day 29 and day 50 is ≥40, for each vaccine strain.
Analysis was performed on the per protocol population.

End point type	Secondary

End point timeframe:

Day 29 and Day 50

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: No statistical analyses for this end point.

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	820	413		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Day 29 (H1N1 strain, N= 818,412)	82 (79 to 84)	81 (77 to 85)		
Day 50 (H1N1 strain, N= 818,412)	98 (96 to 99)	96 (94 to 98)		
Day 29 (H3N2 strain, N= 819,413)	74 (71 to 77)	87 (83 to 90)		
Day 50 (H3N2 strain, N= 819,413)	78 (75 to 80)	87 (84 to 90)		
Day 29 (B strain, N= 820,412)	74 (71 to 77)	73 (68 to 77)		
Day 50 (B strain)	89 (87 to 91)	88 (85 to 91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Adverse Events After Vaccination With Investigational TIV and Control Vaccine

End point title	Number of Subjects Reporting Solicited Adverse Events After Vaccination With Investigational TIV and Control Vaccine

End point description:

The number of 3-17 year old children with solicited local and systemic adverse events and other adverse events, after receiving either one or two doses of investigational TIV as compared to control vaccine are reported.
Analysis was done on the safety set population.

End point type	Secondary

End point timeframe:

Day 1 to 7 after vaccination

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)	TIV (9-17 Yrs)	Control (9-17 yrs)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1037	531	817	412
Units: Number of Subjects				
Any local	364	216	270	148
Injection site pain	363	215	268	146
Injection site ecchymosis	1	1	2	0
Injection site erythema	1	1	2	1
Injection site induration	10	6	5	6
Injection site swelling	11	11	6	3
Any systemic	262	161	193	94
Chills	37	20	38	8
Malaise	77	51	68	27
Myalgia	78	50	54	34
Arthralgia	41	20	26	12
Headache (N=1037,531,817,411)	101	52	93	38
Sweating	37	29	43	22

Fatigue	34	22	52	21
Fever (≥ 38°C)	116	68	39	12
Other	153	89	103	54
Analgesic/Antipyretic med.used(N=1032,531,816,412)	91	52	22	9
Stayed at home due to reaction(N=1019,524,809,411)	93	54	89	49

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited Adverse Events After Vaccination With Investigational TIV and Control Vaccine

End point title	Number of Subjects Reporting Unsolicited Adverse Events After Vaccination With Investigational TIV and Control Vaccine

End point description:

The number of 3-17 year old children reporting any unsolicited adverse event and any serious adverse event (SAE) after receiving either one or two doses of investigational TIV and control vaccine are reported.
Analysis was done on the safety set population.

End point type	Secondary

End point timeframe:

Day 1 to 180 (non-naive)/Day 1 to 209 (naive)

End point values	TIV (3-8Yrs)	Control (3-8 Yrs)	TIV (9-17 Yrs)	Control (9-17 yrs)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1039	531	817	412
Units: Number of Subjects				
Any adverse event	395	194	101	58
At least possibly related adverse event	64	36	23	11
Serious adverse event	14	3	4	3
At least possibly related serious adverse event	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout study

Adverse event reporting additional description:

Solicited adverse events collected from Day 1-7 after each vaccination. Serious adverse events and other unsolicited adverse events were collected from Day 1-180 for non-naive and Day 1-209 for vaccine-naive subjects.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	TIV (3-8 Yrs)

Reporting group description:

The group consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). The non-naive subjects received one dose and naive subjects received two doses of investigational TIV.

Reporting group title	Control (9-17 Yrs)

Reporting group description:

All subjects received one dose of control vaccine (TIVf).

Reporting group title	TIV (9-17 Yrs)

Reporting group description:

All subjects received one dose of investigational TIV.

Reporting group title	Control (3-8 Yrs)

Reporting group description:

The group [control (4-8 years) + control (3 to<4 years)] consisted of naive (who have never received influenza vaccination or had received only one influenza vaccine dose in the same season) and non-naive subjects (who had a record of previous influenza vaccination). Subjects (4-<9 years) received TIVf and subjects (3-<4 years) received comparator TIV. The non-naive subjects received one dose and naive subjects received two doses of control vaccine.

Serious adverse events	TIV (3-8 Yrs)	Control (9-17 Yrs)	TIV (9-17 Yrs)
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 1039 (1.35%)	3 / 412 (0.73%)	4 / 817 (0.49%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			

subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Thermal burn			
subjects affected / exposed	0 / 1039 (0.00%)	0 / 412 (0.00%)	0 / 817 (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			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 1039 (0.00%)	0 / 412 (0.00%)	1 / 817 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	1 / 817 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 1039 (0.00%)	1 / 412 (0.24%)	0 / 817 (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
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Amoebiasis			

subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Appendicitis			
subjects affected / exposed	0 / 1039 (0.00%)	1 / 412 (0.24%)	0 / 817 (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
Ascariasis			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Bronchopneumonia			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Cholera			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Dengue fever			
subjects affected / exposed	1 / 1039 (0.10%)	1 / 412 (0.24%)	1 / 817 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Gastroenteritis bacterial			

subjects affected / exposed	2 / 1039 (0.19%)	0 / 412 (0.00%)	0 / 817 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 1039 (0.00%)	0 / 412 (0.00%)	0 / 817 (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
Measles			
subjects affected / exposed	1 / 1039 (0.10%)	0 / 412 (0.00%)	0 / 817 (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
Pneumonia			
subjects affected / exposed	0 / 1039 (0.00%)	0 / 412 (0.00%)	1 / 817 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 1039 (0.19%)	0 / 412 (0.00%)	0 / 817 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Track Infection Bacterial			
subjects affected / exposed	0 / 1039 (0.00%)	0 / 412 (0.00%)	1 / 817 (0.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control (3-8 Yrs)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 531 (0.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 531 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Soft tissue injury				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	1 / 531 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Asthma				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicide attempt				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Amoebiasis				

subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascariasis				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholera				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue fever				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis bacterial				

subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 531 (0.19%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Measles				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary Track Infection Bacterial				
subjects affected / exposed	0 / 531 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	TIV (3-8 Yrs)	Control (9-17 Yrs)	TIV (9-17 Yrs)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	586 / 1039 (56.40%)	179 / 412 (43.45%)	362 / 817 (44.31%)
Nervous system disorders			
Headache			
subjects affected / exposed	106 / 1039 (10.20%)	39 / 412 (9.47%)	94 / 817 (11.51%)
occurrences (all)	130	44	115
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	34 / 1039 (3.27%)	21 / 412 (5.10%)	52 / 817 (6.36%)
occurrences (all)	37	27	60
Injection site pain			
subjects affected / exposed	363 / 1039 (34.94%)	146 / 412 (35.44%)	268 / 817 (32.80%)
occurrences (all)	471	280	284
Malaise			
subjects affected / exposed	77 / 1039 (7.41%)	27 / 412 (6.55%)	68 / 817 (8.32%)
occurrences (all)	89	32	74
Pyrexia			
subjects affected / exposed	158 / 1039 (15.21%)	14 / 412 (3.40%)	43 / 817 (5.26%)
occurrences (all)	190	17	47
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	37 / 1039 (3.56%)	22 / 412 (5.34%)	43 / 817 (5.26%)
occurrences (all)	41	27	47
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	79 / 1039 (7.60%)	34 / 412 (8.25%)	54 / 817 (6.61%)
occurrences (all)	89	37	61
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	88 / 1039 (8.47%)	11 / 412 (2.67%)	19 / 817 (2.33%)
occurrences (all)	101	11	19
Upper respiratory tract infection			
subjects affected / exposed	99 / 1039 (9.53%)	7 / 412 (1.70%)	14 / 817 (1.71%)
occurrences (all)	118	7	14

Non-serious adverse events	Control (3-8 Yrs)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	309 / 531 (58.19%)		
Nervous system disorders			
Headache			
subjects affected / exposed	54 / 531 (10.17%)		
occurrences (all)	63		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	22 / 531 (4.14%) 26 215 / 531 (40.49%) 151 52 / 531 (9.79%) 61 91 / 531 (17.14%) 119		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	29 / 531 (5.46%) 41		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	51 / 531 (9.60%) 62		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	39 / 531 (7.34%) 49 42 / 531 (7.91%) 45		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to GCP non-compliance at the Mexico site, data of 312 subjects (3-8 year olds) enrolled from this site were excluded from the final immunogenicity and safety analysis.

Notes: