Clinical trial results:
A Randomized, Single-blind, Dose-Ranging Study to Evaluate Immunogenicity, Safety and Tolerability of Different Formulations of Adjuvanted and Nonadjuvanted Cell-derived, Inactivated Novel Swine Origin A/H1N1 Monovalent Subunit Influenza Virus Vaccine in Healthy Subjects from 6 Months to 17 Years of Age.

Summary

EudraCT number	2009-013640-37
Trial protocol	DE NL BE
Global end of trial date	10 August 2011

Results information

Result version number	v2 (current)
This version publication date	28 July 2016
First version publication date	01 January 2015
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	V110_04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00971100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	Via Fiorentina 1, Siena, Italy, 53100
Public contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000663-PIP01-09
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	16 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the preferred vaccine formulation (with or without MF59), dosage (of antigen and adjuvant) and schedule (one or two administrations) of the cell-derived H1N1 swine (sw) monovalent vaccine in healthy children and adolescents based on CHMP criteria and pairwise statistical comparisons for immunogenicity, safety and tolerability.

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	19 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Belgium: 228
Country: Number of subjects enrolled	Germany: 239
Country: Number of subjects enrolled	Dominican Republic: 189
Worldwide total number of subjects	666
EEA total number of subjects	477

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)	240
Children (2-11 years)	316
Adolescents (12-17 years)	110
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at seven sites in Germany, two sites in Belgium, one site in the Netherlands, two sites in Dominican Republic

Pre-assignment

Screening details:

Subjects were enrolled in an age-descending manner and stratified into 4 age cohorts: 9 to 17 years (cohort 1), 3 to 8 years (cohort 2), 12 to 35 months (cohort 3), and 6 to 11 months (cohort 4).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (3.75_Half MF59)

Arm description:

Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25 mLdoses of H1N1 vaccine (3.75mcg of H1N1 and half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm.

Arm title	Cohort 1 (7.5_Full MF59)

Arm description:

Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (7.5mcg of H1N1 and full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm.

Arm title	Cohort 2 (3.75_Half MF59)

Arm description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed

by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25 mLdoses of H1N1 vaccine (3.75mcg of H1N1 and half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm.

Arm title	Cohort 2 (7.5_Full MF59)

Arm description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (7.5mcg of H1N1 and full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm.

Arm title	Cohort 2 (15_No MF59)

Arm description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (15mcg of H1N1 without MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm.

Arm title	Cohort 3 (3.75_Half MF59)

Arm description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25 mLdoses of H1N1 vaccine (3.75mcg of H1N1 and half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm for subjects ≥24 months of age. For subjects aged ≤ 24 months, the injections were administered in the anterolateral aspect of thigh.

Arm title	Cohort 3 (7.5_Full MF59)

Arm description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (7.5mcg of H1N1 and full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm for subjects ≥24 months of age. For subjects aged ≤ 24 months, the injections were administered in the anterolateral aspect of thigh.

Arm title	Cohort 3 (15_No MF59)

Arm description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (15mcg of H1N1 without MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV; all injections were administered IM in the deltoid muscle preferably of the non-dominant arm for subjects ≥24 months of age. For subjects aged ≤ 24 months, the injections were administered in the anterolateral aspect of thigh.

Arm title	Cohort 4 (3.75_Half MF59)

Arm description:

Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental
Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.25 mLdoses of H1N1 vaccine (3.75mcg of H1N1 and half MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV. For subjects aged ≤ 24 months, the injections were administered in the anterolateral aspect of thigh.

Arm title	Cohort 4 (7.5_Full MF59)

Arm description:

Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Arm type	Experimental

Investigational medicinal product name	H1N1 Vaccine
Investigational medicinal product code	V110
Other name	FCC-H1N1sw
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Vaccination consisted of two 0.5 mLdoses of H1N1 vaccine (7.5mcg of H1N1 and full MF59) administered 3 weeks apart followed by one dose of 0.5mL booster vaccination with aTIV. For subjects aged ≤ 24 months, the injections were administered in the anterolateral aspect of thigh.

Number of subjects in period 1	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Started	80	79	72
Completed	23	24	30
Not completed	57	55	42
Consent withdrawn by subject	5	3	4
Adverse Event	2	-	-
Administrative Reason	48	51	32
Lost to follow-up	1	1	5
Unable to Classify	-	-	1
Protocol deviation	1	-	-

Number of subjects in period 1	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Started	73	39	65
Completed	35	14	41
Not completed	38	25	24
Consent withdrawn by subject	7	8	8
Adverse Event	1	1	1
Administrative Reason	30	13	11
Lost to follow-up	-	3	4
Unable to Classify	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort 3 (7.5_Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Started	73	34	75
Completed	49	21	66
Not completed	24	13	9
Consent withdrawn by subject	11	3	4
Adverse Event	-	1	1
Administrative Reason	10	5	3
Lost to follow-up	2	2	1
Unable to Classify	-	1	-

Protocol deviation	1	1	-

Number of subjects in period 1	Cohort 4 (7.5_Full MF59)
Started	76
Completed	61
Not completed	15
Consent withdrawn by subject	9
Adverse Event	1
Administrative Reason	4
Lost to follow-up	-
Unable to Classify	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	
Reporting group title	Cohort 1 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (15_No MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (15_No MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	

Reporting group values	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Number of subjects	80	79	72
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: months			
arithmetic mean	13.2	13.2	5.5
standard deviation	± 2.7	± 2.7	± 1.9
Gender categorical Units: Subjects			
Female	41	37	45
Male	39	42	27

Reporting group values	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Number of subjects	73	39	65
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: months			
arithmetic mean	5.3	5.2	21.8
standard deviation	± 1.7	± 1.5	± 7.3
Gender categorical Units: Subjects			
Female	31	25	34
Male	42	14	31

Reporting group values	Cohort 3 (7.5_Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Number of subjects	73	34	75
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: months			
arithmetic mean	23.1	23.1	8.9
standard deviation	± 7.1	± 7.8	± 1.5
Gender categorical			
Units: Subjects			
Female	27	14	40
Male	46	20	35

Reporting group values	Cohort 4 (7.5_Full MF59)	Total	
Number of subjects	76	666	
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: months			
arithmetic mean	8.8		
standard deviation	± 1.7	-	
Gender categorical			
Units: Subjects			
Female	42	336	
Male	34	330	

End points

End points reporting groups

Reporting group title	Cohort 1 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).	

Reporting group title	Cohort 1 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 2 (15_No MF59)
Reporting group description:	
Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 3 (15_No MF59)
Reporting group description:	
Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (3.75_Half MF59)
Reporting group description:	
Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Reporting group title	Cohort 4 (7.5_Full MF59)
Reporting group description:	
Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.	
Subject analysis set title	Per protocol set- day 366
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum samples at relevant time points (day 366) and who had no major protocol violations as pre-specified in the analysis plan	
Subject analysis set title	Per protocol set- day 387
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum	

samples at relevant time points (day 387) and who had no major protocol violations as pre-specified in the analysis plan

Subject analysis set title	Per protocol set- Day 43
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who received all the relevant doses of vaccine correctly and provided evaluable serum samples at relevant time points (day 43) and who had no major protocol violations as pre-specified in the analysis plan

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in the All Exposed Set who provided post-baseline safety data.

Subject analysis set title	All Cohorts (7.5_Full MF59)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects from all the cohorts receiving H1N1 vaccine (7.5 mcg+full MF59) were pooled.

Subject analysis set title	All Cohorts (3.75_Half MF59)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects from all the cohorts receiving H1N1 vaccine (3.75 mcg+half MF59) were pooled.

Primary: 1. Percentages of subjects achieving seroconversion against A/H1N1 Strain as measured by hemagglutination inhibition (HI) assay.

End point title	1. Percentages of subjects achieving seroconversion against A/H1N1 Strain as measured by hemagglutination inhibition (HI) assay.

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving seroconversion or significant increase in HI titer against the vaccine strain, 3 weeks after receiving 2 doses of vaccination according to CHMP criterion.

Seroconversion is defined as HI ≥40 for subjects negative at baseline [<10] or at least 4-fold increase in HI titer for those positive at baseline [≥10]) on day 22 and day 43.

There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the percentage of subjects achieving seroconversion or at least 4-fold increase in HI antibody (at day 43) is >40%.

End point type	Primary

End point timeframe:

Day 43 (3 weeks post second vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	58	60
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 43	99 (93 to 100)	100 (95 to 100)	100 (94 to 100)	100 (94 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	51	53	25
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 43	97 (83 to 100)	98 (90 to 100)	100 (93 to 100)	84 (64 to 95)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	54		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 43	98 (91 to 100)	100 (93 to 100)		

Statistical analyses

Statistical analysis title	Cohort 1: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated.	
Comparison groups	Cohort 1 (7.5_Full MF59) v Cohort 1 (3.75_Half MF59)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group differences
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	1

Statistical analysis title	Cohort 2: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (7.5_Full MF59)

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Cohort 2: 3.75_Half MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	9

Statistical analysis title	Cohort 2: 7.5_Full MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	9

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	2

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 15_No MF59
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	29

Statistical analysis title	Cohort 3: 7.5_Full MF59 vs 15_No MF59
Statistical analysis description: The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (7.5_Full MF59) v Cohort 3 (15_No MF59)

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	2
upper limit	30

Statistical analysis title	Cohort 4: 3.75_Half MF59 vs 7.5_Full MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	2

Primary: 2. Percentages of subjects achieving HI titers ≥1:40 against A/H1N1 Strain.

End point title	2. Percentages of subjects achieving HI titers ≥1:40 against A/H1N1 Strain.

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving HI titers ≥1: 40 against A/H1N1 strain, 3 weeks after receiving 2 doses of vaccination according to CHMP criterion.

There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the percentage of subjects achieving HI antibody titer ≥ 1:40 is >70% (at day 43).

End point type	Primary

End point timeframe:

Day 43 (3 weeks post second vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	58	60
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	6 (2 to 14)	3 (0 to 10)	0 (0 to 6)	2 (0.042 to 9)
Day 43	100 (95 to 100)	100 (95 to 100)	100 (94 to 100)	100 (94 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	51	53	25
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	0 (0 to 11)	12 (4 to 24)	13 (5 to 25)	20 (7 to 41)
Day 43	97 (83 to 100)	100 (93 to 100)	100 (93 to 100)	88 (69 to 97)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	54		
Units: Percentages of subjects				
number (confidence interval 95%)				
Day 1	17 (9 to 29)	17 (8 to 29)		
Day 43	100 (94 to 100)	100 (93 to 100)		

Statistical analyses

Statistical analysis title	Cohort 1: 3.75_Half MF59 vs 7.5_Full MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 1 (3.75_Half MF59) v Cohort 1 (7.5_Full MF59)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group differences
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Cohort 2: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (7.5_Full MF59)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Cohort 2: 3.75_Half MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (15_No MF59) v Cohort 2 (3.75_Half MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	9

Statistical analysis title	Cohort 2: 7.5_Full MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	9

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 7.5_Full MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 15_No MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	25

Statistical analysis title	Cohort 3: 7.5_Full MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (7.5_Full MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	25

Statistical analysis title	Cohort 4: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Primary: 3. Geometric mean ratios against A/H1N1 strain following 2-dose vaccination schedule as determined by HI assay

End point title	3. Geometric mean ratios against A/H1N1 strain following 2-dose vaccination schedule as determined by HI assay

End point description:

Immunogenicity was measured in terms of geometric mean ratios. The ratio of postvaccination to prevaccination HI GMTs, 3 weeks after second vaccination was reported.

There are no predefined CHMP criteria for the pediatric population however, the criterion is met if the geometric mean ratio (day 43/day 1) in HI antibody titer is >2.5.

End point type	Primary

End point timeframe:

Day 1 and Day 43 (3 weeks post second vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	71	58	60
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	47 (36 to 61)	80 (61 to 103)	86 (67 to 111)	115 (91 to 147)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	51	53	25
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	28 (21 to 38)	89 (54 to 145)	108 (69 to 169)	11 (6.23 to 20)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	54		
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 43/Day 1	92 (51 to 166)	129 (72 to 232)		

Statistical analyses

Statistical analysis title	Cohort 1: 3.75_Half MF59 vs 7.5_Full MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 1 (3.75_Half MF59) v Cohort 1 (7.5_Full MF59)

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.82

Statistical analysis title	Cohort 2: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (7.5_Full MF59)
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1

Statistical analysis title	Cohort 2: 3.75_MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (3.75_Half MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.16
upper limit	4.35

Statistical analysis title	Cohort 2: 7.5_Full MF59 vs 15_no MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 2 (7.5_Full MF59) v Cohort 2 (15_No MF59)
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	4.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.91
upper limit	5.81

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 7.5_Full MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (3.75_Half MF59) v Cohort 3 (7.5_Full MF59)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.29

Statistical analysis title	Cohort 3: 3.75_Half MF59 vs 15_No MF59
Statistical analysis description:	
The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated	
Comparison groups	Cohort 3 (15_No MF59) v Cohort 3 (3.75_Half MF59)

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.53
upper limit	14

Statistical analysis title	Cohort 3: 7.5_Full MF 59 vs 15_No MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 3 (7.5_Full MF59) v Cohort 3 (15_No MF59)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	9.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.51
upper limit	17

Statistical analysis title	Cohort 4: 3.75_Half MF59 vs 7.5_Full MF59

Statistical analysis description:

The statistical significance for the differences in immune responses between vaccine groups on day 43 was calculated

Comparison groups	Cohort 4 (3.75_Half MF59) v Cohort 4 (7.5_Full MF59)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
Method	ANOVA
Parameter estimate	Vaccine group ratios
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.08

Primary: 4. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Any Primary Vaccination

End point title	4. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Any Primary Vaccination[1]

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic adverse events, 3 weeks after the primary course with H1N1sw monovalent vaccine.

End point type	Primary

End point timeframe:

From day 1 through day 7 after any vaccination.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	79	71	72
Units: Number				
Ecchymosis (N=79,79,71,72,39,65,73,33,75,74)	5	7	9	9
Erythema (N=79,79,71,72,39,65,73,33,75,74)	10	16	14	23
Induration (N=79,79,71,72,39,65,73,33,75,74)	13	15	8	16
Swelling (N=79,79,71,72,39,65,73,33,75,74)	9	13	9	11
Tenderness (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Pain (N=79,79,70,72,39,65,73,33,75,74)	61	67	39	40
Chills (N=79,79,70,72,39,0,0,0,0,0)	3	10	3	7
Malaise (N=79,79,70,72,39,0,0,0,0,0)	10	16	12	5
Myalgia (N=79,79,70,72,39,0,0,0,0,0)	21	21	6	10
Arthralgia (N=79,79,70,72,39,0,0,0,0,0)	12	10	5	6
Headache (N=79,79,70,72,39,0,0,0,0,0)	22	25	7	8
Sweating (N=79,79,70,72,39,0,0,0,0,0)	5	3	1	1
Fatigue (N=79,79,70,72,39,0,0,0,0,0)	23	25	21	17
Nausea(N=79,79,70,72,39,0,0,0,0,0)	9	8	5	6
Diarrhea (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Sleepiness (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Vomiting (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Irritability (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Chang. eating habits (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Unus. Crying (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0
Shivering (N=0,0,0,0,0,65,73,33,75,74)	0	0	0	0

Fever (≥38°C) (N=79,79,70,72,39,65,73,33,75,74)	2	1	10	7
Temp (≥40°C) (N=79,79,70,72,39,65,73,33,75,74)	0	0	0	0
Stayed Home (N=79,79,70,72,39,65,73,33,75,74)	4	3	5	13
Analg.Antipy Used (N=79,79,70,72,39,65,73,33,75,74	11	12	11	16

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	65	71	33
Units: Number				
Ecchymosis (N=79,79,71,72,39,65,73,33,75,74)	10	4	10	5
Erythema (N=79,79,71,72,39,65,73,33,75,74)	8	13	17	8
Induration (N=79,79,71,72,39,65,73,33,75,74)	6	8	13	5
Swelling (N=79,79,71,72,39,65,73,33,75,74)	4	2	7	3
Tenderness (N=0,0,0,0,0,65,73,33,75,74)	0	9	36	13
Pain (N=79,79,70,72,39,65,73,33,75,74)	19	0	0	0
Chills (N=79,79,70,72,39,0,0,0,0,0)	2	0	0	0
Malaise (N=79,79,70,72,39,0,0,0,0,0)	7	0	0	0
Myalgia (N=79,79,70,72,39,0,0,0,0,0)	3	0	0	0
Arthralgia (N=79,79,70,72,39,0,0,0,0,0)	2	0	0	0
Headache (N=79,79,70,72,39,0,0,0,0,0)	6	0	0	0
Sweating (N=79,79,70,72,39,0,0,0,0,0)	0	0	0	0
Fatigue (N=79,79,70,72,39,0,0,0,0,0)	8	0	0	0
Nausea(N=79,79,70,72,39,0,0,0,0,0)	3	0	0	0
Diarrhea (N=0,0,0,0,0,65,73,33,75,74)	0	21	24	8
Sleepiness (N=0,0,0,0,0,65,73,33,75,74)	0	17	30	9
Vomiting (N=0,0,0,0,0,65,73,33,75,74)	0	11	18	3
Irritability (N=0,0,0,0,0,65,73,33,75,74)	0	19	18	7
Chang. eating habits (N=0,0,0,0,0,65,73,33,75,74)	0	21	26	6
Unus. Crying (N=0,0,0,0,0,65,73,33,75,74)	0	20	27	10
Shivering (N=0,0,0,0,0,65,73,33,75,74)	0	6	6	2
Fever (≥38°C) (N=79,79,70,72,39,65,73,33,75,74)	3	17	12	5
Temp (≥40°C) (N=79,79,70,72,39,65,73,33,75,74)	0	0	1	0
Stayed Home (N=79,79,70,72,39,65,73,33,75,74)	3	11	10	4
Analg.Antipy Used (N=79,79,70,72,39,65,73,33,75,74	5	28	27	14

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: Number				
Ecchymosis (N=79,79,71,72,39,65,73,33,75,74)	4	0		
Erythema (N=79,79,71,72,39,65,73,33,75,74)	12	7		
Induration (N=79,79,71,72,39,65,73,33,75,74)	6	8		
Swelling (N=79,79,71,72,39,65,73,33,75,74)	1	0		
Tenderness (N=0,0,0,0,0,65,73,33,75,74)	18	26		
Pain (N=79,79,70,72,39,65,73,33,75,74)	0	0		
Chills (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Malaise (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Myalgia (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Arthralgia (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Headache (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Sweating (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Fatigue (N=79,79,70,72,39,0,0,0,0,0)	0	0		
Nausea(N=79,79,70,72,39,0,0,0,0,0)	0	0		
Diarrhea (N=0,0,0,0,0,65,73,33,75,74)	24	32		
Sleepiness (N=0,0,0,0,0,65,73,33,75,74)	14	20		
Vomiting (N=0,0,0,0,0,65,73,33,75,74)	17	18		
Irritability (N=0,0,0,0,0,65,73,33,75,74)	14	13		
Chang. eating habits (N=0,0,0,0,0,65,73,33,75,74)	18	25		
Unus. Crying (N=0,0,0,0,0,65,73,33,75,74)	27	26		
Shivering (N=0,0,0,0,0,65,73,33,75,74)	4	5		
Fever (≥38°C) (N=79,79,70,72,39,65,73,33,75,74)	13	17		
Temp (≥40°C) (N=79,79,70,72,39,65,73,33,75,74)	1	1		
Stayed Home (N=79,79,70,72,39,65,73,33,75,74)	14	11		
Analg.Antipy Used (N=79,79,70,72,39,65,73,33,75,74	28	31		

Statistical analyses

No statistical analyses for this end point

Primary: 5. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Booster Vaccination

End point title	5. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After Booster Vaccination[2]

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic adverse events following booster vaccination, 12 months (day 366) after the first dose of primary vaccination.

End point type	Primary

End point timeframe:

From day 366 through day 372.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	24	30	35
Units: Number				
Ecchymosis	2	0	1	1
Erythema	2	3	8	5
Induration	5	3	4	5
Swelling	0	4	3	5
Inj Site Pain (N=23,24,30,35,14,0,0,0,0,0)	17	19	23	24
Tenderness (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Chills (N=23,24,30,35,14,0,0,0,0,0)	1	1	3	5
Malaise (N=23,24,30,35,14,0,0,0,0,0)	5	3	8	11
Myalgia (N=23,24,30,35,14,0,0,0,0,0)	7	8	4	9
Arthralgia (N=23,24,30,35,14,0,0,0,0,0)	1	2	5	5
Headache (N=23,24,30,35,14,0,0,0,0,0)	5	5	10	11
Sweating (N=23,24,30,35,14,0,0,0,0,0)	2	2	2	3
Fatigue (N=23,24,30,35,14,0,0,0,0,0)	4	2	7	10
Nausea (N=23,24,30,35,14,0,0,0,0,0)	4	2	4	6
Sleepiness (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Diarrhea (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Vomiting (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Irritability (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Chg. In eating habits (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Shivering (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Unus. Crying (N=0,0,0,0,0,42,51,21,67,61)	0	0	0	0
Fever (≥38°C)	1	0	0	8
Temp (≥40°C)	0	0	0	0
Stayed Home (N=23,24,30,35,14,41,50,21,67,61)	3	2	3	10
Analg.Antipy. Med. Used	4	3	4	8

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	42	51	21
Units: Number				
Ecchymosis	0	2	5	0
Erythema	0	6	13	4
Induration	0	4	7	3
Swelling	1	6	4	1
Inj Site Pain (N=23,24,30,35,14,0,0,0,0,0)	9	0	0	0
Tenderness (N=0,0,0,0,0,42,51,21,67,61)	0	8	18	7
Chills (N=23,24,30,35,14,0,0,0,0,0)	0	0	0	0
Malaise (N=23,24,30,35,14,0,0,0,0,0)	0	0	0	0
Myalgia (N=23,24,30,35,14,0,0,0,0,0)	4	0	0	0
Arthralgia (N=23,24,30,35,14,0,0,0,0,0)	2	0	0	0
Headache (N=23,24,30,35,14,0,0,0,0,0)	1	0	0	0
Sweating (N=23,24,30,35,14,0,0,0,0,0)	0	0	0	0
Fatigue (N=23,24,30,35,14,0,0,0,0,0)	1	0	0	0
Nausea (N=23,24,30,35,14,0,0,0,0,0)	1	0	0	0
Sleepiness (N=0,0,0,0,0,42,51,21,67,61)	0	9	6	1
Diarrhea (N=0,0,0,0,0,42,51,21,67,61)	0	6	4	1
Vomiting (N=0,0,0,0,0,42,51,21,67,61)	0	1	2	0
Irritability (N=0,0,0,0,0,42,51,21,67,61)	0	5	3	3
Chg. In eating habits (N=0,0,0,0,0,42,51,21,67,61)	0	5	4	1
Shivering (N=0,0,0,0,0,42,51,21,67,61)	0	1	3	0
Unus. Crying (N=0,0,0,0,0,42,51,21,67,61)	0	3	4	1
Fever (≥38°C)	0	6	15	2
Temp (≥40°C)	0	1	0	1
Stayed Home (N=23,24,30,35,14,41,50,21,67,61)	0	5	1	2
Analg.Antipy. Med. Used	1	8	15	5

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	61		
Units: Number				
Ecchymosis	1	1		
Erythema	5	9		
Induration	5	4		
Swelling	1	5		

Inj Site Pain (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Tenderness (N=0,0,0,0,0,42,51,21,67,61)	11	19		
Chills (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Malaise (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Myalgia (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Arthralgia (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Headache (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Sweating (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Fatigue (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Nausea (N=23,24,30,35,14,0,0,0,0,0)	0	0		
Sleepiness (N=0,0,0,0,0,42,51,21,67,61)	5	10		
Diarrhea (N=0,0,0,0,0,42,51,21,67,61)	8	6		
Vomiting (N=0,0,0,0,0,42,51,21,67,61)	2	1		
Irritability (N=0,0,0,0,0,42,51,21,67,61)	3	6		
Chg. In eating habits (N=0,0,0,0,0,42,51,21,67,61)	2	7		
Shivering (N=0,0,0,0,0,42,51,21,67,61)	3	2		
Unus. Crying (N=0,0,0,0,0,42,51,21,67,61)	4	9		
Fever (≥38°C)	9	13		
Temp (≥40°C)	1	0		
Stayed Home (N=23,24,30,35,14,41,50,21,67,61)	5	5		
Analg.Antipy. Med. Used	13	19		

Statistical analyses

No statistical analyses for this end point

Primary: 6. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After second seasonal flu Vaccination

End point title	6. Number of Subjects Reporting Solicited Local and Systemic Adverse Events, After second seasonal flu Vaccination[3][4]

End point description:

Safety was assessed as the number of subjects who reported solicited local and systemic adverse events. For subjects aged <9 years of age at the time of booster received a second seasonal flu dose on day 387 for influenza vaccine naive subjects.

End point type	Primary

End point timeframe:

Day 387 through day 394

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

[4] - 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	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	26	11	36
Units: Number				
Injection Site Ecchymosis	0	1	0	0
Injection Site Erythema	4	6	0	10
Injection Site Induration	4	7	0	8
Injection Site Swelling	4	5	1	7
Injection Site Pain (N=22,26,11,0,0,0,0,0)	13	13	7	0
Tenderness (N=0,0,0,36,45,17,63,60)	0	0	0	8
Chills (N=22,26,11,0,0,0,0,0)	0	1	0	0
Malaise (N=22,26,11,0,0,0,0,0)	1	2	1	0
Myalgia (N=22,26,11,0,0,0,0,0)	1	2	1	0
Arthralgia (N=22,26,11,0,0,0,0,0)	1	2	1	0
Headache (N=22,26,11,0,0,0,0,0)	3	3	1	0
Sweating (N=22,26,11,0,0,0,0,0)	0	1	0	0
Fatigue (N=22,26,11,0,0,0,0,0)	3	6	2	0
Nausea (N=22,26,11,0,0,0,0,0)	1	2	1	0
Sleepiness (N=0,0,0,36,45,17,63,60)	0	0	0	1
Diarrhoea (N=0,0,0,36,45,17,63,60)	0	0	0	3
Vomiting (N=0,0,0,36,45,17,63,60)	0	0	0	1
Irritability (N=0,0,0,36,45,17,63,60)	0	0	0	2
Chg. In eating habits (N=0,0,0,36,45,17,63,60)	0	0	0	3
Shivering (N=0,0,0,36,45,17,63,60)	0	0	0	1
Unus. Crying (N=0,0,0,36,45,17,63,60)	0	0	0	1
Fever (≥38°C)	1	2	1	3
Temp (≥40°C)	0	0	0	0
Stayed Home	1	0	0	1
Analg.Antipy. Med. Used	2	6	1	3

End point values	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	17	63	60
Units: Number				
Injection Site Ecchymosis	1	1	1	1
Injection Site Erythema	10	2	6	6
Injection Site Induration	8	3	6	5
Injection Site Swelling	7	2	3	3
Injection Site Pain (N=22,26,11,0,0,0,0,0)	0	0	0	0
Tenderness (N=0,0,0,36,45,17,63,60)	11	4	14	13
Chills (N=22,26,11,0,0,0,0,0)	0	0	0	0
Malaise (N=22,26,11,0,0,0,0,0)	0	0	0	0
Myalgia (N=22,26,11,0,0,0,0,0)	0	0	0	0
Arthralgia (N=22,26,11,0,0,0,0,0)	0	0	0	0
Headache (N=22,26,11,0,0,0,0,0)	0	0	0	0
Sweating (N=22,26,11,0,0,0,0,0)	0	0	0	0

Fatigue (N=22,26,11,0,0,0,0,0)	0	0	0	0
Nausea (N=22,26,11,0,0,0,0,0)	0	0	0	0
Sleepiness (N=0,0,0,36,45,17,63,60)	1	1	3	5
Diarrhoea (N=0,0,0,36,45,17,63,60)	3	0	7	7
Vomiting (N=0,0,0,36,45,17,63,60)	1	0	5	2
Irritability (N=0,0,0,36,45,17,63,60)	3	3	4	2
Chg. In eating habits (N=0,0,0,36,45,17,63,60)	2	1	6	5
Shivering (N=0,0,0,36,45,17,63,60)	0	0	2	1
Unus. Crying (N=0,0,0,36,45,17,63,60)	3	1	8	3
Fever (≥38°C)	4	0	7	10
Temp (≥40°C)	0	0	0	0
Stayed Home	0	0	2	3
Analg.Antipy. Med. Used	6	1	10	11

Statistical analyses

No statistical analyses for this end point

Primary: 7. Number of Subjects Reporting Unsolicited Adverse Events after primary and booster vaccination.

End point title	7. Number of Subjects Reporting Unsolicited Adverse Events after primary and booster vaccination.[5]

End point description:

Safety was assessed as the number of subjects who reported unsolicited adverse events after primary vaccination and following booster vaccination, 12 months (day 366) after the first dose of primary vaccination. For influenza vaccine naive subjects aged <9 years of age at the time of booster received a second seasonal flu dose on day 387.
All AEs were collected from day 1 to day 43 after primary vaccination, from day 366 through day 387 after booster vaccination and day 387 to day 401 for subjects who receive second seasonal flu dose

End point type	Primary

End point timeframe:

Day 1 through day 43, day 366 through day 387, day 387 through day 401.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	79	71	72
Units: Number				
Any AE-Primary vacc.;79,79,71,72,39,65,73,33,75,74	28	26	31	31
Possibly related AEs-79,79,71,72,39,65,73,33,75,74	15	18	15	18
Any AE-booster vacc.;74,78,80,80,37,65,74,30,75,73	3	4	6	6
Possibly related AEs-74,78,80,80,37,65,74,30,75,73	2	1	2	3
Any AE-2nd seasonal;0,0,30,35,14,41,50,21,66,60	0	0	1	5

Possibly related AEs-0,0,30,35,14,41,50,21,66,60	0	0	0	0

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	65	71	33
Units: Number				
Any AE-Primary vacc.;79,79,71,72,39,65,73,33,75,74	17	33	32	23
Possibly related AEs-79,79,71,72,39,65,73,33,75,74	11	4	9	7
Any AE-booster vacc.;74,78,80,80,37,65,74,30,75,73	1	5	10	2
Possibly related AEs-74,78,80,80,37,65,74,30,75,73	0	1	4	1
Any AE-2nd seasonal;0,0,30,35,14,41,50,21,66,60	1	1	8	2
Possibly related AEs-0,0,30,35,14,41,50,21,66,60	0	0	2	0

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: Number				
Any AE-Primary vacc.;79,79,71,72,39,65,73,33,75,74	51	50		
Possibly related AEs-79,79,71,72,39,65,73,33,75,74	20	22		
Any AE-booster vacc.;74,78,80,80,37,65,74,30,75,73	20	16		
Possibly related AEs-74,78,80,80,37,65,74,30,75,73	6	4		
Any AE-2nd seasonal;0,0,30,35,14,41,50,21,66,60	14	17		
Possibly related AEs-0,0,30,35,14,41,50,21,66,60	3	3		

Statistical analyses

No statistical analyses for this end point

Primary: 8. Number of Subjects Reporting Unsolicited Adverse Events.

End point title	8. Number of Subjects Reporting Unsolicited Adverse Events.[6]

End point description:

Safety was assessed as the number of subjects who reported unsolicited adverse events.

SAEs, new onset of chronic diseases, AEs leading to withdrawal from the study were collected from day 1 to day 546 following 2-dose vaccination H1N1sw monovalent vaccine

End point type	Primary

End point timeframe:

SAEs, NOCDs, AEs leading to withdrawal-day 1 to day 546

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	79	72	73
Units: Number				
Any SAEs	3	2	1	3
At least possibly related SAEs	0	1	0	0
AEs leading to discontinuation	2	0	0	1
New onset of chronic disease	0	3	0	0

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	65	71	34
Units: Number				
Any SAEs	0	7	8	5
At least possibly related SAEs	0	0	1	0
AEs leading to discontinuation	1	1	0	1
New onset of chronic disease	0	0	0	1

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	76		
Units: Number				
Any SAEs	11	8		
At least possibly related SAEs	1	0		
AEs leading to discontinuation	1	1		
New onset of chronic disease	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Percentages of subjects achieving seroconversion against A/H1N1 Strain following a booster dose as measured by hemagglutination inhibition (HI) assay.

End point title	9. Percentages of subjects achieving seroconversion against A/H1N1 Strain following a booster dose as measured by hemagglutination inhibition (HI) assay.

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving seroconversion or significant increase in HI titer against the A/H1N1 strain, after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion.

At least one CHMP criterion as assessed three weeks after the booster dose should be met within each age cohort to fulfill regulatory requirements.

End point type	Secondary

End point timeframe:

Day 387 (3 weeks post booster vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	20	20	29
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 387 (From Day 366)	89 (67 to 99)	80 (56 to 94)	95 (75 to 100)	100 (88 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	32	38	17
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 387 (From Day 366)	100 (69 to 100)	94 (79 to 99)	95 (82 to 99)	100 (80 to 100)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 387 (From Day 366)	85 (72 to 94)	90 (76 to 97)		

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Percentages of subjects achieving HI titers ≥1:40 agianst A/H1N1 Strain following a booster dose

End point title	10. Percentages of subjects achieving HI titers ≥1:40 agianst A/H1N1 Strain following a booster dose

End point description:

Immunogenicity was measured in terms of percentage of subjects achieving HI titers ≥1:40 against A/H1N1 strain after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion.

At least one CHMP criterion as assessed three weeks after the booster dose should be met within each age cohort to fulfill regulatory requirements.

End point type	Secondary

End point timeframe:

Day 366 and Day 387 (3 weeks post second vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	22	24	31
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 366	86 (64 to 97)	95 (77 to 100)	100 (86 to 100)	100 (89 to 100)
Day 387 (N=19,20,20,29,10,32,38,17,47,40)	100 (82 to 100)	100 (83 to 100)	100 (83 to 100)	100 (88 to 100)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	39	46	21
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 366	91 (59 to 100)	100 (91 to 100)	100 (92 to 100)	71 (48 to 89)
Day 387 (N=19,20,20,29,10,32,38,17,47,40)	100 (69 to 100)	100 (89 to 100)	100 (91 to 100)	100 (80 to 100)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	47		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 366	94 (85 to 99)	100 (92 to 100)		
Day 387 (N=19,20,20,29,10,32,38,17,47,40)	100 (92 to 100)	100 (91 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Geometric mean Ratios against A/H1N1 strain following a booster dose as determined by HI assay

End point title	11. Geometric mean Ratios against A/H1N1 strain following a booster dose as determined by HI assay

End point description:

Immunogenicity was measured in terms of geometric mean ratios. The ratio of postvaccination to prevaccination HI GMTs after a booster dose with aTIV, administered 12 months after primary vaccination according to CHMP criterion was assessed.

End point type	Secondary

End point timeframe:

Day 366 and Day 387 (3 weeks post booster vaccination)

End point values	Cohort 1 (3.75_Half	Cohort 1 (7.5_Full	Cohort 2 (3.75_Half	Cohort 2 (7.5_Full
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	20	20	29
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 387/Day 366	15 (6.89 to 33)	8.47 (4.34 to 17)	28 (15 to 51)	26 (16 to 43)

End point values	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half	Cohort 3 (7.5_Full	Cohort 3 (15_No MF59)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	32	38	17
Units: Ratios				
geometric mean (confidence interval 95%)				
Day 387/Day 366	30 (14 to 62)	19 (9.73 to 39)	17 (8.88 to 31)	36 (16 to 81)

End point values	Cohort 4 (3.75_Half	Cohort 4 (7.5_Full		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	40		
Units: Ratios				

geometric mean (confidence interval 95%)				
Day 387/Day 366	33 (17 to 63)	23 (11 to 46)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12. Geometric mean titers against A/H1N1 strain as determined by HI assay in pooled population

End point title	12. Geometric mean titers against A/H1N1 strain as determined by HI assay in pooled population

End point description:

Immunogenicity was measured in terms of geometric mean titers against A/H1N1 strain, 3 weeks after second vaccination in pooled children population.

End point type	Secondary

End point timeframe:

Day 1 and Day 43 (3 weeks post second vaccination)

End point values	All Cohorts (7.5_Full MF59)	All Cohorts (3.75_Half MF59)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	238	239		
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	7.55 (6.03 to 9.45)	7.75 (6.16 to 9.75)		
Day 43	756 (633 to 902)	539 (449 to 646)		

Statistical analyses

Statistical analysis title	Difference in HI GMTs of half and full dose MF59

Statistical analysis description:

To demonstrate the non-inferiority of immune response in terms of GMTs in subjects receiving 3.75 HA and half MF59, versus subjects receiving 7.5 HA and full MF59, 3 weeks after second vaccination.

Comparison groups	All Cohorts (7.5_Full MF59) v All Cohorts (3.75_Half MF59)
Number of subjects included in analysis	477
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	ANOVA
Parameter estimate	Vaccine group difference
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.85

Notes:

[7] - Non-inferiority will be concluded if the lower limit of the two sided 95% CI for the between group difference (3.75_Half MF59-7.5_Full MF59) in terms of post-immunization GMTs (at day 43) is higher or equal to 0.5.
If the hypothesis above can be rejected the same non-inferiority hypothesis were to be tested using a non-inferiority margin of 0.67.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 546

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Cohort 1 (3.75_Half MF59)

Reporting group description:

Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an adjuvanted trivalent influenza vaccine (aTIV).

Reporting group title	Cohort 1 (7.5_Full MF59)

Reporting group description:

Subjects aged ≥9 to ≤17 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 2 (3.75_Half MF59)

Reporting group description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 2 (7.5_Full MF59)

Reporting group description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 2 (15_No MF59)

Reporting group description:

Subjects aged ≥3 to ≤8 years received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (3.75_Half MF59)

Reporting group description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (7.5_Full MF59)

Reporting group description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 3 (15_No MF59)

Reporting group description:

Subjects aged ≥12 to ≤35 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 4 (3.75_Half MF59)

Reporting group description:

Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Reporting group title	Cohort 4 (7.5_Full MF59)

Reporting group description:

Subjects aged ≥6 to ≤11 months received 2 doses of H1N1 vaccine administered 3 weeks apart, followed by a booster dose 12 months after first vaccination with an aTIV.

Serious adverse events	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 79 (3.80%)	2 / 79 (2.53%)	1 / 71 (1.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	0 / 71 (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
Toxicity to various agents			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	0 / 71 (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
Concussion			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental exposure			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Chemical poisoning			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
Convulsion			

subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	0 / 71 (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
Febrile convulsion			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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 cyst			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	0 / 71 (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
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Gastritis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Asthma			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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 congestion			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Bronchospasm			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
Suicidal ideation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	0 / 71 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
Appendicitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	0 / 71 (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			

subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Acute tonsillitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Amoebic dysentery			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Dengue fever			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Giardiasis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Laryngitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Tonsillitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Upper respiratory tract infection			

subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Urinary tract infection			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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
Bronchiolitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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 rotavirus			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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 syncytial virus bronchiolitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (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 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 72 (4.17%)	0 / 39 (0.00%)	7 / 65 (10.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint Dislocation			

subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Toxicity to various agents			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Concussion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Skull fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Accidental exposure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Chemical poisoning			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
Convulsion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Epilepsy			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Migraine			

subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Febrile convulsion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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 cyst			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
Vomiting			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Gastritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Asthma			

subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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 congestion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
Suicidal ideation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
subjects affected / exposed	1 / 72 (1.39%)	0 / 39 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 72 (2.78%)	0 / 39 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute tonsillitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Amoebic dysentery			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Giardiasis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Laryngitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Tonsillitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Urinary tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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
Bronchiolitis			

subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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 rotavirus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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 syncytial virus bronchiolitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	0 / 65 (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 (7.5_Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 73 (10.96%)	5 / 33 (15.15%)	11 / 75 (14.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Toxicity to various agents			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Concussion			

subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Skull fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Accidental exposure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	0 / 75 (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
Chemical poisoning			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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			
Convulsion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Epilepsy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Migraine			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Febrile convulsion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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 cyst			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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			
Vomiting			
subjects affected / exposed	2 / 73 (2.74%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
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			
Adenoidal hypertrophy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	0 / 75 (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
Asthma			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	2 / 75 (2.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract congestion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Bronchospasm			

subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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			
Suicidal ideation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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			
Appendicitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (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			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	4 / 75 (5.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (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
Acute tonsillitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	0 / 75 (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
Amoebic dysentery			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	3 / 75 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dengue fever			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Giardiasis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	0 / 75 (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
Laryngitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (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
Tonsillitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (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
Urinary tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (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
Bronchiolitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
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 rotavirus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 33 (0.00%)	0 / 75 (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

Serious adverse events	Cohort 4 (7.5_Full MF59)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 74 (10.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint Dislocation			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Accidental exposure			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chemical poisoning			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract congestion			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Acute tonsillitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Amoebic dysentery			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Giardiasis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngitis			

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 74 (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 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchiolitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis rotavirus				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 74 (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	Cohort 1 (3.75_Half MF59)	Cohort 1 (7.5_Full MF59)	Cohort 2 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 79 (89.87%)	72 / 79 (91.14%)	63 / 71 (88.73%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	28 / 79 (35.44%)	29 / 79 (36.71%)	17 / 71 (23.94%)
occurrences (all)	42	47	24
Somnolence			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 79 (3.80%)	10 / 79 (12.66%)	6 / 71 (8.45%)
occurrences (all)	4	12	7
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 79 (31.65%)	28 / 79 (35.44%)	26 / 71 (36.62%)
occurrences (all)	35	40	38
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 79 (15.19%)	18 / 79 (22.78%)	24 / 71 (33.80%)
occurrences (all)	12	20	30
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 79 (7.59%)	7 / 79 (8.86%)	10 / 71 (14.08%)
occurrences (all)	10	9	13
Injection site induration			

alternative assessment type: Systematic			
subjects affected / exposed	18 / 79 (22.78%)	17 / 79 (21.52%)	15 / 71 (21.13%)
occurrences (all)	21	20	18
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	62 / 79 (78.48%)	67 / 79 (84.81%)	49 / 71 (69.01%)
occurrences (all)	115	131	96
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 79 (11.39%)	17 / 79 (21.52%)	15 / 71 (21.13%)
occurrences (all)	9	21	17
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 79 (17.72%)	20 / 79 (25.32%)	20 / 71 (28.17%)
occurrences (all)	17	27	23
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 79 (5.06%)	1 / 79 (1.27%)	19 / 71 (26.76%)
occurrences (all)	5	1	26
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 79 (3.80%)	1 / 79 (1.27%)	3 / 71 (4.23%)
occurrences (all)	3	2	5
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 79 (8.86%)	1 / 79 (1.27%)	5 / 71 (7.04%)
occurrences (all)	8	1	6
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 79 (16.46%)	10 / 79 (12.66%)	10 / 71 (14.08%)
occurrences (all)	14	11	10
Vomiting			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 79 (1.27%)	0 / 79 (0.00%)	2 / 71 (2.82%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 79 (3.80%)	2 / 79 (2.53%)	4 / 71 (5.63%)
occurrences (all)	3	2	4
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 79 (1.27%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	6 / 79 (7.59%)	5 / 79 (6.33%)	3 / 71 (4.23%)
occurrences (all)	9	7	3
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 79 (16.46%)	12 / 79 (15.19%)	10 / 71 (14.08%)
occurrences (all)	13	15	13
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	28 / 79 (35.44%)	28 / 79 (35.44%)	10 / 71 (14.08%)
occurrences (all)	32	32	12
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 79 (2.53%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences (all)	2	0	1
Conjunctivitis			

subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 79 (1.27%)	3 / 79 (3.80%)	3 / 71 (4.23%)
occurrences (all)	2	4	3
Rhinitis			
subjects affected / exposed	6 / 79 (7.59%)	6 / 79 (7.59%)	5 / 71 (7.04%)
occurrences (all)	6	7	5
Tonsillitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 79 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 79 (5.06%)	1 / 79 (1.27%)	5 / 71 (7.04%)
occurrences (all)	4	1	5

Non-serious adverse events	Cohort 2 (7.5_Full MF59)	Cohort 2 (15_No MF59)	Cohort 3 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 72 (91.67%)	34 / 39 (87.18%)	61 / 65 (93.85%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 72 (23.61%)	9 / 39 (23.08%)	0 / 65 (0.00%)
occurrences (all)	24	11	0
Somnolence			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	21 / 65 (32.31%)
occurrences (all)	0	0	41
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 72 (15.28%)	2 / 39 (5.13%)	7 / 65 (10.77%)
occurrences (all)	13	2	10
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 39 (0.00%)	21 / 65 (32.31%)
occurrences (all)	0	0	34
Fatigue			

alternative assessment type: Systematic			
subjects affected / exposed	24 / 72 (33.33%)	10 / 39 (25.64%)	0 / 65 (0.00%)
occurrences (all)	46	19	0
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	28 / 72 (38.89%)	8 / 39 (20.51%)	22 / 65 (33.85%)
occurrences (all)	40	10	33
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 72 (15.28%)	10 / 39 (25.64%)	6 / 65 (9.23%)
occurrences (all)	13	13	6
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 72 (29.17%)	6 / 39 (15.38%)	17 / 65 (26.15%)
occurrences (all)	34	6	22
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	49 / 72 (68.06%)	23 / 39 (58.97%)	22 / 65 (33.85%)
occurrences (all)	103	42	32
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	19 / 72 (26.39%)	5 / 39 (12.82%)	13 / 65 (20.00%)
occurrences (all)	22	6	16
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 72 (20.83%)	8 / 39 (20.51%)	0 / 65 (0.00%)
occurrences (all)	21	16	0
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 72 (33.33%)	6 / 39 (15.38%)	37 / 65 (56.92%)
occurrences (all)	48	7	60
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 72 (2.78%)	3 / 39 (7.69%)	0 / 65 (0.00%)
occurrences (all)	2	5	0
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 72 (8.33%)	3 / 39 (7.69%)	24 / 65 (36.92%)
occurrences (all)	8	5	41
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 72 (13.89%)	4 / 39 (10.26%)	0 / 65 (0.00%)
occurrences (all)	15	8	0
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 72 (6.94%)	2 / 39 (5.13%)	12 / 65 (18.46%)
occurrences (all)	27	2	19
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 72 (2.78%)	3 / 39 (7.69%)	0 / 65 (0.00%)
occurrences (all)	2	3	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 72 (0.00%)	2 / 39 (5.13%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Hyperhidrosis			
subjects affected / exposed	4 / 72 (5.56%)	0 / 39 (0.00%)	0 / 65 (0.00%)
occurrences (all)	6	0	0
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	2 / 72 (2.78%)	0 / 39 (0.00%)	23 / 65 (35.38%)
occurrences (all)	2	0	36
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 72 (5.56%)	2 / 39 (5.13%)	21 / 65 (32.31%)
occurrences (all)	5	2	37
Musculoskeletal and connective tissue disorders			

Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	11 / 72 (15.28%)	4 / 39 (10.26%)	0 / 65 (0.00%)
occurrences (all)	14	5	0
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	20 / 72 (27.78%)	7 / 39 (17.95%)	0 / 65 (0.00%)
occurrences (all)	26	10	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 39 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	2 / 72 (2.78%)	0 / 39 (0.00%)	1 / 65 (1.54%)
occurrences (all)	2	0	1
Nasopharyngitis			
subjects affected / exposed	2 / 72 (2.78%)	1 / 39 (2.56%)	15 / 65 (23.08%)
occurrences (all)	4	1	20
Rhinitis			
subjects affected / exposed	7 / 72 (9.72%)	1 / 39 (2.56%)	4 / 65 (6.15%)
occurrences (all)	9	1	4
Tonsillitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 39 (0.00%)	3 / 65 (4.62%)
occurrences (all)	2	0	3
Upper respiratory tract infection			
subjects affected / exposed	3 / 72 (4.17%)	3 / 39 (7.69%)	1 / 65 (1.54%)
occurrences (all)	4	3	1

Non-serious adverse events	Cohort 3 (7.5_Full MF59)	Cohort 3 (15_No MF59)	Cohort 4 (3.75_Half MF59)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 73 (89.04%)	28 / 33 (84.85%)	70 / 75 (93.33%)
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0

Somnolence			
subjects affected / exposed	35 / 73 (47.95%)	9 / 33 (27.27%)	17 / 75 (22.67%)
occurrences (all)	49	13	33
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 73 (13.70%)	2 / 33 (6.06%)	5 / 75 (6.67%)
occurrences (all)	10	2	10
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 73 (39.73%)	10 / 33 (30.30%)	32 / 75 (42.67%)
occurrences (all)	47	13	54
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 73 (41.10%)	10 / 33 (30.30%)	16 / 75 (21.33%)
occurrences (all)	53	16	26
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	15 / 73 (20.55%)	6 / 33 (18.18%)	6 / 75 (8.00%)
occurrences (all)	20	8	9
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	23 / 73 (31.51%)	8 / 33 (24.24%)	10 / 75 (13.33%)
occurrences (all)	32	11	18
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	44 / 73 (60.27%)	17 / 33 (51.52%)	29 / 75 (38.67%)
occurrences (all)	90	32	50
Injection site swelling			
alternative assessment type: Systematic			

subjects affected / exposed	16 / 73 (21.92%)	5 / 33 (15.15%)	3 / 75 (4.00%)
occurrences (all)	20	6	42
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	38 / 73 (52.05%)	12 / 33 (36.36%)	32 / 75 (42.67%)
occurrences (all)	63	19	42
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 33 (3.03%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	30 / 73 (41.10%)	10 / 33 (30.30%)	35 / 75 (46.67%)
occurrences (all)	43	15	68
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 73 (34.25%)	4 / 33 (12.12%)	21 / 75 (28.00%)
occurrences (all)	27	6	33
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	33 / 73 (45.21%)	8 / 33 (24.24%)	24 / 75 (32.00%)
occurrences (all)	42	14	37
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 73 (28.77%)	7 / 33 (21.21%)	15 / 75 (20.00%)
occurrences (all)	35	13	26
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 73 (0.00%)	0 / 33 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 73 (2.74%)	3 / 33 (9.09%)	2 / 75 (2.67%)
occurrences (all)	2	4	2
Conjunctivitis			
subjects affected / exposed	1 / 73 (1.37%)	1 / 33 (3.03%)	2 / 75 (2.67%)
occurrences (all)	1	1	3
Nasopharyngitis			
subjects affected / exposed	16 / 73 (21.92%)	13 / 33 (39.39%)	40 / 75 (53.33%)
occurrences (all)	18	14	64
Rhinitis			
subjects affected / exposed	2 / 73 (2.74%)	1 / 33 (3.03%)	1 / 75 (1.33%)
occurrences (all)	2	1	1
Tonsillitis			
subjects affected / exposed	5 / 73 (6.85%)	0 / 33 (0.00%)	6 / 75 (8.00%)
occurrences (all)	6	0	6
Upper respiratory tract infection			

subjects affected / exposed	4 / 73 (5.48%)	0 / 33 (0.00%)	1 / 75 (1.33%)
occurrences (all)	4	0	1

Non-serious adverse events	Cohort 4 (7.5_Full MF59)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 74 (93.24%)		
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	28 / 74 (37.84%)		
occurrences (all)	48		
General disorders and administration site conditions			
Chills			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	9		
Crying			
alternative assessment type: Systematic			
subjects affected / exposed	31 / 74 (41.89%)		
occurrences (all)	52		
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 74 (21.62%)		
occurrences (all)	24		
Injection site haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	2		

Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	19		
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 74 (45.95%)		
occurrences (all)	69		
Injection site swelling			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	8		
Malaise			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	39 / 74 (52.70%)		
occurrences (all)	66		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	38 / 74 (51.35%)		
occurrences (all)	84		
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Vomiting			
alternative assessment type: Systematic			

subjects affected / exposed	22 / 74 (29.73%)		
occurrences (all)	31		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	27 / 74 (36.49%)		
occurrences (all)	55		
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	17 / 74 (22.97%)		
occurrences (all)	27		
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Conjunctivitis			

subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	33 / 74 (44.59%)		
occurrences (all)	46		
Rhinitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	To allow interim analysis of the study, if there is a request in public health interest.
07 April 2010	To address the change that the booster will be administered using the egg-derived, seasonal, trivalent MF59 adjuvanted vaccine

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported