Clinical trial results:
Pivotal, Multicenter, Observer-Blind, Randomized Study of Influenza A (H1N1) 2009 Monovalent Subunit Vaccine With and Without Adjuvant in Children Ages 6 to <36 Months

Summary

EudraCT number	2014-005107-24
Trial protocol	Outside EU/EEA
Global end of trial date	06 December 2010

Results information

Result version number	v2 (current)
This version publication date	29 July 2016
First version publication date	12 April 2015
Version creation reason	• Correction of full data set Required for the re-QC because of EudraCT system glitch as possible updates to results are required. Moreover, the study is now transferred to another primary user.

Trial information

Trial identification

Sponsor protocol code	V112_06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00996307
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate hemagglutination inhibition (HI) assay results for each vaccine group after 1 and 2 doses and according to immunogenicity criteria defined by CBER recommendations.
To evaluate the safety and tolerability of each A/H1N1 2009 vaccine group in this young pediatric population.

Protection of trial subjects:

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

Background therapy:

Test vaccines were supplied as a single prefilled syringe containing 15µg A/H1N1 2009 antigen per 0.5mL dose. The adjuvant was supplied separately as prefilled vials containing approximately 0.7mL of MF59 at approximately 27.3mg of squalene per vial. Adjuvanted vaccines were prepared by bedside mixing of the contents in prefilled syringes of A/H1N1 2009 antigen and MF59 adjuvant. All the vaccine were administered intramuscularly (IM) at study days 1 and 22 (3 weeks after first vaccination) within the pre-specified visit windows.

Evidence for comparator:

There were no reference vaccines in this study.

Actual start date of recruitment	01 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason, Safety
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mexico: 40
Country: Number of subjects enrolled	United States: 614
Worldwide total number of subjects	654
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	348
Children (2-11 years)	306
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 29 sites in USA and Mexico.

Pre-assignment

Screening details:

All subjects enrolled were included in the trial.

Period 1

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

Blinding implementation details:

Observer-blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	3.75_(50)MF59

Arm description:

3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Arm type	Experimental
Investigational medicinal product name	Monovalent H1N1 influenza virus vaccine with MF59 adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.25mL dose/IM

Arm title	7.5_(0)MF59

Arm description:

7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Arm type	Experimental
Investigational medicinal product name	Monovalent H1N1 influenza virus vaccine without MF59 adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.25mL dose/IM

Arm title	7.5_(50)MF59

Arm description:

7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Arm type	Experimental

Investigational medicinal product name	Monovalent H1N1 influenza virus vaccine with MF59 adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.38mL dose/IM

Arm title	15_(0)MF59

Arm description:

15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Arm type	Experimental
Investigational medicinal product name	Monovalent H1N1 influenza virus vaccine without MF59 adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL dose/IM

Number of subjects in period 1	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59
Started	164	165	160
Completed	144	148	146
Not completed	20	17	14
Consent withdrawn by subject	3	2	5
Unable to classify	4	-	2
Adverse event	-	1	-
Lost to follow-up	13	13	7
Administrative reason	-	1	-

Number of subjects in period 1	15_(0)MF59
Started	165
Completed	144
Not completed	21
Consent withdrawn by subject	5
Unable to classify	1
Adverse event	-
Lost to follow-up	15
Administrative reason	-

Baseline characteristics

Reporting groups	
Reporting group title	3.75_(50)MF59
Reporting group description:	
3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(0)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(50)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	15_(0)MF59
Reporting group description:	
15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	

Reporting group values	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59
Number of subjects	164	165	160
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	21.2	21.6	21.1
standard deviation	± 7.9	± 8.8	± 8.4
Gender categorical Units: Subjects			
Female	75	79	80
Male	89	86	80

Reporting group values	15_(0)MF59	Total	
Number of subjects	165	654	
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	21.3		
standard deviation	± 8.9	-	
Gender categorical			
Units: Subjects			
Female	78	312	
Male	87	342	

End points

End points reporting groups

Reporting group title	3.75_(50)MF59
Reporting group description:	
3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(0)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(50)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	15_(0)MF59
Reporting group description:	
15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	
Subject analysis set title	All enrolled set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects enrolled in this study.	
Subject analysis set title	Full Analysis Set (FAS), Immunogenicity
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the All Randomized Set who: - Actually received a study vaccination AND - Provided at least one evaluable serum sample for immunogenicity testing before and after baseline In case the study vaccination was not performed according to the subject's randomization, subjects were to be analyzed as randomized in the FAS.	
Subject analysis set title	Per Protocol Set (PPS), Immunogenicity
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the FAS who were considered "evaluable" which included subjects who: - Received all study vaccinations correctly AND - Provided evaluable serum sample for immunogenicity testing at the relevant timepoints (day 1, day 22, and/or day 43), AND - Had no major protocol deviation as pre-specified in the Analysis Plan. A major protocol deviation was defined as a protocol deviation that was considered to have a significant impact on the analysis of the subject's antibody responses.	
Subject analysis set title	Safety Set, Overall
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set who had at least one safety observation (e.g., data regarding local/systemic reactions, AEs) following study vaccination.	
Subject analysis set title	3.75_(50)MF59 - No Previous Vaccination
Subject analysis set type	Per protocol
Subject analysis set description:	
3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22 in subjects who did not receive a previous seasonal influenza vaccination.	
Subject analysis set title	7.5_(0)MF59 - No Previous Vaccination
Subject analysis set type	Per protocol
Subject analysis set description:	
7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22 in subjects who did not receive a previous seasonal influenza vaccination.	
Subject analysis set title	7.5_(50)MF59 - No Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22 in subjects who did not receive a previous seasonal influenza vaccination.

Subject analysis set title	15_(0)MF59 - No Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22 in subjects who did not receive a previous seasonal influenza vaccination.

Subject analysis set title	3.75_(50)MF59 - Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22 in subjects who had received a previous seasonal influenza vaccination.

Subject analysis set title	7.5_(0)MF59 - Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22 in subjects who had received a previous seasonal influenza vaccination.

Subject analysis set title	7.5_(50) MF59 - Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22 who had received a previous seasonal influenza vaccination.

Subject analysis set title	15_(0)MF59 - Previous Vaccination
Subject analysis set type	Per protocol

Subject analysis set description:

15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22 who had received a previous seasonal influenza vaccination.

Subject analysis set title	3.75_(50)MF59 - Baseline HI <1:10
Subject analysis set type	Per protocol

Subject analysis set description:

3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	7.5_(0)MF59 - Baseline HI <1:10
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	7.5_(50)MF59 - Baseline HI <1:10
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	15_(0)MF59 - Baseline HI <1:10
Subject analysis set type	Per protocol

Subject analysis set description:

15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	3.75_(50)MF59 - Baseline HI ≥1:10
Subject analysis set type	Per protocol

Subject analysis set description:

3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	7.5_(0)MF59 - Baseline HI ≥1:10
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	7.5_(50)MF59 - Baseline HI ≥1:10
Subject analysis set type	Per protocol

Subject analysis set description:

7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.

Subject analysis set title	15_(0)MF59 - Baseline HI ≥1:10
Subject analysis set type	Per protocol

Subject analysis set description:

15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.

Primary: 1. Antibody Responses After the First and Second Vaccinations.

End point title	1. Antibody Responses After the First and Second

End point description:

CBER guidance (<65 years of age): The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should be ≥ 40% AND the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should be ≥ 70%.

End point type	Primary

End point timeframe:

21 days after each 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	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59	15_(0)MF59
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	124	126	129
Units: Percentages of subjects				
number (confidence interval 95%)				
HI titer ≥1:40 (Baseline)	19 (12 to 26)	9 (5 to 15)	15 (9 to 23)	19 (13 to 27)
HI titer ≥1:40 (Day 22)	79 (71 to 86)	37 (29 to 46)	86 (78 to 91)	50 (41 to 59)
Seroconversion Day 22	74 (65 to 81)	32 (24 to 41)	80 (72 to 87)	44 (35 to 53)
HI titer ≥1:40 (Day 43)	100 (97 to 100)	70 (61 to 78)	100 (97 to 100)	81 (74 to 88)
Seroconversion Day 43	98 (93 to 100)	68 (59 to 76)	98 (94 to 100)	76 (68 to 83)
HI titer ≥1:40 (Day 202; N=45,38,46,38)	96 (85 to 99)	50 (33 to 67)	100 (92 to 100)	55 (38 to 71)
Seroconversion Day 202; N=45,38,46,38)	89 (76 to 96)	50 (33 to 67)	91 (79 to 98)	39 (24 to 57)
HI titer ≥1:40 (Day 387; N=46,37,38,36)	85 (71 to 94)	27 (14 to 44)	84 (69 to 94)	36 (21 to 54)
Seroconversion Day 387; N=45,38,46,38)	76 (61 to 87)	22 (10 to 38)	76 (60 to 89)	25 (12 to 42)

Statistical analyses

No statistical analyses for this end point

Primary: 2. Number of Participants Reporting Solicited Local and Systemic Reactions After First Vaccination.

End point title	2. Number of Participants Reporting Solicited Local and Systemic Reactions After First Vaccination.[2]

End point description:

Safety was measured in terms of the number of participants reporting solicited local and systemic

reactions after first vaccination.

End point type	Primary

End point timeframe:

Day 1 to 7

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	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59	15_(0)MF59
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	161	161	160[3]	162
Units: Number of subjects				
Ecchymosis	0	0	0	0
Erythema	1	0	2	1
Swelling	6	9	4	6
Induration	8	8	13	8
Tenderness	49	42	53	42
Sleepiness	36	28	38	30
Diarrhea	32	28	37	25
Vomiting	13	10	12	10
Irritability	40	39	45	41
Change in eating habits	21	16	19	18
Persist crying	34	35	35	35
Fever (rectal temp ≥38.5°C)	5	5	9	7

Notes:

[3] - Actual number subjects analysed in this group was 161

Statistical analyses

No statistical analyses for this end point

Primary: 3. Number of Participants Reporting Solicited Local and Systemic Reactions After Second Vaccination.

End point title	3. Number of Participants Reporting Solicited Local and Systemic Reactions After Second Vaccination.[4]

End point description:

Safety was measured in terms of the number of participants reporting solicited local and systemic reactions after second vaccination.

End point type	Primary

End point timeframe:

Day 22 to 28

Notes:

[4] - 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	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59	15_(0)MF59
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	155	148	157	157
Units: Number of subjects				
Ecchymosis (N=154,147,155,156)	0	0	1	0
Erythema (N=155,147,157,157)	1	1	4	1
Swelling	2	1	8	6
Induration	4	3	12	9
Tenderness (N=155,148,156,157)	35	27	37	32
Sleepiness	28	21	20	17
Diarrhea	20	19	20	15
Vomiting	11	9	14	5
Irritabilty	36	39	32	24
change in eating habits	20	18	14	11
Persist crying	21	22	24	18
Fever (rectal temp ≥38.5°C)	8	5	4	7

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Immunogenicity Measurement by Geometric Mean Titers (GMT).

End point title	4. Immunogenicity Measurement by Geometric Mean Titers (GMT).

End point description:

Immunogenicity was measured in terms of the GMT at 21 days after each vaccination.

End point type	Secondary

End point timeframe:

21 days after each vaccination

End point values	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59	15_(0)MF59
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	124	126	129
Units: Titers				
geometric mean (confidence interval 95%)				
GMT Baseline	10 (7.94 to 14)	7.27 (5.5 to 9.6)	9.29 (7.06 to 12)	11 (8.22 to 14)
GMT Day 22	83 (56 to 123)	20 (14 to 31)	92 (62 to 136)	37 (25 to 55)
GMT Day 43	642 (468 to 879)	80 (58 to 110)	626 (457 to 858)	151 (110 to 206)

Statistical analyses

Statistical analysis title	1. Immunogenicity measurement by GMT

Statistical analysis description:

The two-sided confidence intervals (CIs) were calculated and assessed for non-inferiority first against the margin of 0.5 (exploratory margin) and in case of success against the margin of 0.667 (based on CBER guidance against the licensed comparator).
Day 22

Comparison groups	3.75_(50)MF59 v 7.5_(0)MF59
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Ratio of GMTs
Point estimate	4.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.55
upper limit	6.46

Notes:

[5] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS.

Statistical analysis title	2. Immunogenicity measurement by GMT

Statistical analysis description:

The two-sided CIs were calculated and assessed for non-inferiority first against the margin of 0.5 (exploratory margin) and in case of success against the margin of 0.667 (based on CBER guidance against the licensed comparator).
Day 22

Comparison groups	3.75_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Ratio of GMTs
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.42
upper limit	3.56

Notes:

[6] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on PPS.

Statistical analysis title	3. Immunogenicity measurement by GMT

Statistical analysis description:

The two-sided CIs were calculated and assessed for non-inferiority first against the margin of 0.5 (exploratory margin) and in case of success against the margin of 0.667 (based on CBER guidance against the licensed comparator).
Day 22

Comparison groups	7.5_(50)MF59 v 7.5_(0)MF59

Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Ratio of GMTs
Point estimate	4.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	7.19

Notes:

[7] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on PPS.

Statistical analysis title	4. Immunogenicity measurement by GMT

Statistical analysis description:

The two-sided confidence intervals (CIs) were calculated and assessed for non-inferiority first against the margin of 0.5 (exploratory margin) and in case of success against the margin of 0.667 (based on CBER guidance against the licensed comparator).
Day 22

Comparison groups	7.5_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Ratio of GMTs
Point estimate	2.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	3.96

Notes:

[8] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS.

Statistical analysis title	5. Immunogenicity measurement by GMT

Statistical analysis description:

Non-inferiority of adjuvanted vaccines was demonstrated against the non-adjuvanted vaccines in terms of antibody titers if the lower bound of the 2-sided 95% CI of GMT ratios were greater than 0.5 (exploratory margin) and also greater than 0.667 (based on CBER guidance against the licensed comparator).
Day 43

Comparison groups	3.75_(50)MF59 v 7.5_(0)MF59
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Ratio of GMTs
Point estimate	8.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.52
upper limit	12

Notes:

[9] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS

Statistical analysis title	6. Immunogenicity measurement by GMT

Statistical analysis description:

Non-inferiority of adjuvanted vaccines was demonstrated against the non-adjuvanted vaccines in terms of antibody titers if the lower bound of the 2-sided 95% CI of GMT ratios were greater than 0.5 (exploratory margin) and also greater than 0.667 (based on CBER guidance against the licensed comparator).
Day 43

Comparison groups	3.75_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Ratio of GMTs
Point estimate	4.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.94
upper limit	6.15

Notes:

[10] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS

Statistical analysis title	7. Immunogenicity measurement by GMT

Statistical analysis description:

Non-inferiority of adjuvanted vaccines was demonstrated against the non-adjuvanted vaccines in terms of antibody titers if the lower bound of the 2-sided 95% CI of GMT ratios were greater than 0.5 (exploratory margin) and also greater than 0.667 (based on CBER guidance against the licensed comparator).
Day 43

Comparison groups	7.5_(50)MF59 v 7.5_(0)MF59
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	Ratio of GMTs
Point estimate	7.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.36
upper limit	11

Notes:

[11] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS.

Statistical analysis title	8. Immunogenicity measurement by GMT

Statistical analysis description:

Non-inferiority of adjuvanted vaccines was demonstrated against the non-adjuvanted vaccines in terms of antibody titers if the lower bound of the 2-sided 95% CI of GMT ratios were greater than 0.5 (exploratory margin) and also greater than 0.667 (based on CBER guidance against the licensed comparator).
Day 43

Comparison groups	7.5_(50)MF59 v 15_(0)MF59

Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Ratio of GMTs
Point estimate	4.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.86
upper limit	6.02

Notes:

[12] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on PPS

Statistical analysis title	9. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 22.

Comparison groups	3.75_(50)MF59 v 7.5_(0)MF59
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Ratio of GMTs
Point estimate	3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.37
upper limit	5.65

Notes:

[13] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	10. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 22.

Comparison groups	3.75_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Ratio of GMTs
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	3.4

Notes:

[14] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	11. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 22.

Comparison groups	7.5_(50)MF59 v 7.5_(0)MF59
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[15]
Parameter estimate	Ratio of GMTs
Point estimate	4.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.85
upper limit	6.86

Notes:

[15] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	12. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 22.

Comparison groups	7.5_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[16]
Parameter estimate	Ratio of GMTs
Point estimate	2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.72
upper limit	4.13

Notes:

[16] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	13. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 43.

Comparison groups	7.5_(0)MF59 v 3.75_(50)MF59
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[17]
Parameter estimate	Ratio of GMTs
Point estimate	7.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.54
upper limit	11

Notes:

[17] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	14. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 43.

Comparison groups	3.75_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[18]
Parameter estimate	Ratio of GMTs
Point estimate	4.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.23
upper limit	6.42

Notes:

[18] - Log10-transformed HI antibody responses were to be modeled using analysis of variance (ANOVA) including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	15. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 43.

Comparison groups	7.5_(0)MF59 v 7.5_(50)MF59
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[19]
Parameter estimate	Ratio of GMTs
Point estimate	7.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	11

Notes:

[19] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Statistical analysis title	16. Immunogenicity measurement by GMT

Statistical analysis description:

Superiority of the adjuvanted vaccines against the non-adjuvanted vaccines was to be tested against the margin of 1 on day 43.

Comparison groups	7.5_(50)MF59 v 15_(0)MF59
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[20]
Parameter estimate	Ratio of GMTs
Point estimate	4.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.09
upper limit	6.19

Notes:

[20] - Log10-transformed HI antibody responses were to be modeled using ANOVA including factor for vaccine group and center. Analysis done on FAS.

Secondary: 5. Antibody Responses in Subjects With and Without Seasonal Influenza Vaccination for Year 2009 to 2010.

End point title	5. Antibody Responses in Subjects With and Without Seasonal Influenza Vaccination for Year 2009 to 2010.

End point description:

Subgroup analysis based on receipt of recent seasonal vaccination. Comparison between subjects previously vaccinated versus not vaccinated with seasonal influenza vaccines.

End point type	Secondary

End point timeframe:

Day 22 (three weeks after first vaccination); day 43 (three weeks after second vaccination)

End point values	3.75_(50)MF59 - No Previous Vaccination	7.5_(0)MF59 - No Previous Vaccination	7.5_(50)MF59 - No Previous Vaccination	15_(0)MF59 - No Previous Vaccination
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	83	92	89
Units: Percentages of subjects				
number (confidence interval 95%)				
Seroconversion (Day 22)	73 (62 to 82)	37 (27 to 49)	78 (68 to 86)	44 (33 to 55)
Seroconversion (Day 43)	99 (93 to 100)	66 (55 to 76)	98 (92 to 100)	78 (67 to 86)
HI titer ≥1:40 (Day 1)	25 (16 to 36)	12 (6 to 21)	16 (9 to 25)	21 (13 to 31)
HI titer ≥1:40 (Day 22)	78 (67 to 86)	42 (31 to 54)	84 (75 to 91)	49 (39 to 60)
HI titer ≥1:40 (Day 43)	100 (96 to 100)	67 (56 to 77)	100 (96 to 100)	83 (74 to 90)

End point values	3.75_(50)MF59 - Previous Vaccination	7.5_(0)MF59 - Previous Vaccination	7.5_(50) MF59 - Previous Vaccination	15_(0)MF59 - Previous Vaccination
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	41	34	40
Units: Percentages of subjects				
number (confidence interval 95%)				
Seroconversion (Day 22)	75 (60 to 86)	22 (11 to 38)	86 (70 to 95)	45 (29 to 62)
Seroconversion (Day 43)	96 (86 to 99)	71 (54 to 84)	100 (90 to 100)	73 (56 to 85)
HI titer ≥1:40 (Day 1)	8 (2 to 20)	2 (0.062 to 13)	14 (5 to 30)	15 (6 to 30)
HI titer ≥1:40 (Day 22)	81 (67 to 91)	27 (14 to 43)	91 (77 to 98)	50 (34 to 66)
HI titer ≥1:40 (Day 43)	100 (93 to 100)	76 (60 to 88)	100 (90 to 100)	78 (62 to 89)

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Geometric Mean Titers (GMTs) in Subjects With and Without Seasonal Influenza Vaccination for Year 2009 to 2010.

End point title	6. Geometric Mean Titers (GMTs) in Subjects With and Without Seasonal Influenza Vaccination for Year 2009 to 2010.

End point description:

Subgroup analysis based on receipt of recent seasonal vaccination. Comparison between subjects previously vaccinated versus not vaccinated with seasonal influenza vaccines.

End point type	Secondary

End point timeframe:

Day 22 (three weeks after first vaccination); day 43 (three weeks after second vaccination)

End point values	3.75_(50)MF59 - No Previous Vaccination	7.5_(0)MF59 - No Previous Vaccination	7.5_(50)MF59 - No Previous Vaccination	15_(0)MF59 - No Previous Vaccination
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	81	83	92	89
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	11 (7.66 to 16)	7.95 (5.58 to 11)	9.94 (6.93 to 14)	12 (8.3 to 17)
Day 22	101 (61 to 167)	25 (15 to 41)	105 (63 to 173)	42 (26 to 68)
Day 43	975 (663 to 1432)	103 (71 to 149)	788 (538 to 1154)	186 (129 to 271)

End point values	3.75_(50)MF59 - Previous Vaccination	7.5_(0)MF59 - Previous Vaccination	7.5_(50) MF59 - Previous Vaccination	15_(0)MF59 - Previous Vaccination
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	41	34	40
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	10 (6.84 to 15)	6.52 (4.28 to 9.94)	8.3 (5.46 to 13)	10 (6.58 to 15)
Day 22	80 (43 to 148)	17 (8.88 to 34)	100 (51 to 194)	45 (23 to 87)
Day 43	389 (226 to 669)	57 (32 to 103)	483 (269 to 867)	124 (69 to 224)

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Antibody Response Based on Baseline Seropositivity.

End point title	7. Antibody Response Based on Baseline Seropositivity.

End point description:

Subgroup analysis based on Subjects with a pre-vaccination HI antibody titer < 1:10 and pre-vaccination HI antibody titer ≥ 1:10
Immunogenicity responses in subjects who are seropositive (A/H1N1 2009 HI titer ≥ 1:10) at Baseline (Day 1 (pre-vaccination)) as compared to those who are seronegative (HI titer < 1:10)

End point type	Secondary

End point timeframe:

Day 22 (three weeks after first vaccination); day 43 (three weeks after second vaccination)

End point values	3.75_(50)MF59 - Baseline HI <1:10	7.5_(0)MF59 - Baseline HI <1:10	7.5_(50)MF59 - Baseline HI <1:10	15_(0)MF59 - Baseline HI <1:10
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	96	91	90
Units: Percentages of subjects				
number (confidence interval 95%)				
Seroconversion (Day 22)	72 (62 to 81)	31 (22 to 42)	82 (73 to 90)	39 (29 to 50)
Seroconversion (Day 43)	100 (96 to 100)	67 (56 to 76)	100 (96 to 100)	77 (67 to 85)
HI titer ≥1:40 (Day 1)	0 (0 to 4)	0 (0 to 4)	0 (0 to 4)	0 (0 to 4)
HI titer ≥1:40 (Day 22)	72 (62 to 81)	31 (22 to 42)	82 (73 to 90)	39 (29 to 50)
HI titer ≥1:40 (Day 43)	100 (96 to 100)	67 (56 to 76)	100 (96 to 100)	77 (67 to 85)

End point values	3.75_(50)MF59 - Baseline HI ≥1:10	7.5_(0)MF59 - Baseline HI ≥1:10	7.5_(50)MF59 - Baseline HI ≥1:10	15_(0)MF59 - Baseline HI ≥1:10
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	28	35	39
Units: Percentages of subjects				
number (confidence interval 95%)				
Seroconversion (Day 22)	77 (61 to 89)	36 (19 to 56)	74 (57 to 88)	56 (40 to 72)
Seroconversion (Day 43)	92 (79 to 98)	71 (51 to 87)	94 (81 to 99)	74 (58 to 87)
HI titer ≥1:40 (Day 1)	62 (45 to 77)	39 (22 to 59)	54 (37 to 71)	64 (47 to 79)
HI titer ≥1:40 (Day 22)	95 (83 to 99)	57 (37 to 76)	94 (81 to 99)	74 (58 to 87)
HI titer ≥1:40 (Day 43)	100 (91 to 100)	82 (63 to 94)	100 (90 to 100)	92 (79 to 98)

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Geometric Mean Titers (GMTs) Based on Baseline Seropositivity.

End point title	8. Geometric Mean Titers (GMTs) Based on Baseline Seropositivity.

End point description:

Subgroup analysis based on Subjects with a pre-vaccination HI antibody titer < 1:10 and pre-vaccination HI antibody titer ≥ 1:10
Immunogenicity responses in subjects who are seropositive (A/H1N1 2009 HI titer ≥ 1:10) at Baseline (Day 1 (pre-vaccination)) as compared to those who are seronegative (HI titer < 1:10).

End point type	Secondary

End point timeframe:

Day 22 (three weeks after first vaccination); day 43 (three weeks after second vaccination)

End point values	3.75_(50)MF59 - Baseline HI <1:10	7.5_(0)MF59 - Baseline HI <1:10	7.5_(50)MF59 - Baseline HI <1:10	15_(0)MF59 - Baseline HI <1:10
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90	96	91	90
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	5.06 (4.98 to 5.14)	5.07 (4.99 to 5.15)	5.01 (4.93 to 5.09)	5.06 (4.98 to 5.14)
Day 22	42 (29 to 61)	15 (11 to 22)	60 (42 to 88)	17 (12 to 24)
Day 43	566 (398 to 804)	65 (46 to 93)	577 (404 to 825)	96 (67 to 137)

End point values	3.75_(50)MF59 - Baseline HI ≥1:10	7.5_(0)MF59 - Baseline HI ≥1:10	7.5_(50)MF59 - Baseline HI ≥1:10	15_(0)MF59 - Baseline HI ≥1:10
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	28	35	39
Units: Titers				
geometric mean (confidence interval 95%)				
Day 1	53 (34 to 83)	35 (21 to 58)	47 (29 to 76)	69 (44 to 108)
Day 22	266 (137 to 517)	67 (31 to 145)	313 (154 to 639)	248 (126 to 487)
Day 43	660 (390 to 1117)	167 (90 to 308)	811 (462 to 1426)	420 (246 to 717)

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Antibody Persistence by Geometric Mean Titers (GMT).

End point title	9. Antibody Persistence by Geometric Mean Titers (GMT).

End point description:

Immunogenicity was assessed in terms of Geometric Mean Titers (GMT at 6 months (Day 202)and 12 months (Day 387) after second vaccination.

End point type	Secondary

End point timeframe:

6 months (Day 202) and 12 months (Day 387) after second vaccination

End point values	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59	15_(0)MF59
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	129	124	126	129
Units: Titers				
geometric mean (confidence interval 95%)				
GMT (Day 1)	10 (7.94 to 14)	7.27 (5.5 to 9.6)	9.29 (7.06 to 12)	11 (8.22 to 14)
GMT (Day 202; N=45,38,46,38)	176 (111 to 280)	33 (20 to 54)	205 (133 to 316)	42 (25 to 69)
GMT (Day 387; N=46,37,38,36)	92 (52 to 162)	15 (8.24 to 28)	85 (48 to 151)	25 (13 to 46)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study	
Adverse event reporting additional description:	
Local, systemic, and other reactions were collected from Study days 1 to 7 and 22 to 28. Serious adverse events (SAEs), medically attended visits, new onset of chronic diseases and AEs that lead to subject's withdrawal were collected from Day 1 (post-consent) through Day 387 (12 months following second vaccination)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	3.75_(50)MF59
Reporting group description:	
3.75 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(0)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	7.5_(50)MF59
Reporting group description:	
7.5 µg A/H1N1 antigen with 50% MF59 adjuvant administered on study day 1 and day 22.	
Reporting group title	15_(0)MF59
Reporting group description:	
15 µg A/H1N1 antigen without MF59 adjuvant administered on study day 1 and day 22.	

Serious adverse events	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 162 (3.09%)	6 / 164 (3.66%)	1 / 162 (0.62%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	2 / 162 (1.23%)	0 / 164 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (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
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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
Constipation			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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
Intussusception			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (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
Vomiting			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (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
Asthma			

subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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
Hypoxia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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 distress			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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			
Mental status changes			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	0 / 162 (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
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (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
Atypical pneumonia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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
Cellulitis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	0 / 162 (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
Genital abscess			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 162 (0.00%)	1 / 164 (0.61%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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
Staphylococcal abscess			
subjects affected / exposed	1 / 162 (0.62%)	0 / 164 (0.00%)	1 / 162 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 162 (0.00%)	0 / 164 (0.00%)	0 / 162 (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 / 162 (0.00%)	2 / 164 (1.22%)	0 / 162 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	15_(0)MF59		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 166 (6.02%)		
number of deaths (all causes)	0		
number of deaths resulting from	0		

adverse events			
Injury, poisoning and procedural complications			
Accidental exposure to product			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intussusception			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 166 (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 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	0 / 166 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 166 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 166 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 166 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital abscess				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media				
subjects affected / exposed	0 / 166 (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	3 / 166 (1.81%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Staphylococcal abscess				
subjects affected / exposed	0 / 166 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				

subjects affected / exposed	2 / 166 (1.20%)		
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 / 166 (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	3.75_(50)MF59	7.5_(0)MF59	7.5_(50)MF59
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 162 (88.89%)	152 / 164 (92.68%)	141 / 162 (87.04%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	51 / 162 (31.48%)	41 / 164 (25.00%)	48 / 162 (29.63%)
occurrences (all)	71	58	66
General disorders and administration site conditions			
Crying			
subjects affected / exposed	47 / 162 (29.01%)	46 / 164 (28.05%)	48 / 162 (29.63%)
occurrences (all)	62	72	64
Injection site pain			
subjects affected / exposed	60 / 162 (37.04%)	51 / 164 (31.10%)	60 / 162 (37.04%)
occurrences (all)	87	69	95
Pyrexia			
subjects affected / exposed	53 / 162 (32.72%)	52 / 164 (31.71%)	54 / 162 (33.33%)
occurrences (all)	72	81	88
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	9 / 162 (5.56%)	4 / 164 (2.44%)	7 / 162 (4.32%)
occurrences (all)	10	4	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	57 / 162 (35.19%)	52 / 164 (31.71%)	63 / 162 (38.89%)
occurrences (all)	83	85	82

Vomiting			
subjects affected / exposed	33 / 162 (20.37%)	37 / 164 (22.56%)	33 / 162 (20.37%)
occurrences (all)	47	48	41
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 162 (4.32%)	8 / 164 (4.88%)	5 / 162 (3.09%)
occurrences (all)	7	11	8
Bronchial Hyperreactivity			
subjects affected / exposed	6 / 162 (3.70%)	9 / 164 (5.49%)	10 / 162 (6.17%)
occurrences (all)	8	10	14
Cough			
subjects affected / exposed	45 / 162 (27.78%)	54 / 164 (32.93%)	46 / 162 (28.40%)
occurrences (all)	68	75	58
Nasal congestion			
subjects affected / exposed	11 / 162 (6.79%)	11 / 164 (6.71%)	14 / 162 (8.64%)
occurrences (all)	11	11	14
Rhinitis allergic			
subjects affected / exposed	8 / 162 (4.94%)	10 / 164 (6.10%)	5 / 162 (3.09%)
occurrences (all)	12	10	6
Rhinorrhoea			
subjects affected / exposed	26 / 162 (16.05%)	24 / 164 (14.63%)	27 / 162 (16.67%)
occurrences (all)	30	32	32
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	10 / 162 (6.17%)	12 / 164 (7.32%)	8 / 162 (4.94%)
occurrences (all)	10	12	8
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	33 / 162 (20.37%)	30 / 164 (18.29%)	30 / 162 (18.52%)
occurrences (all)	49	40	35
Irritability			
subjects affected / exposed	58 / 162 (35.80%)	62 / 164 (37.80%)	60 / 162 (37.04%)
occurrences (all)	90	102	97
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	10 / 162 (6.17%)	12 / 164 (7.32%)	9 / 162 (5.56%)
occurrences (all)	12	15	10
Bronchitis			
subjects affected / exposed	5 / 162 (3.09%)	6 / 164 (3.66%)	9 / 162 (5.56%)
occurrences (all)	6	6	11
Conjunctivitis			
subjects affected / exposed	27 / 162 (16.67%)	22 / 164 (13.41%)	18 / 162 (11.11%)
occurrences (all)	30	25	19
Croup infectious			
subjects affected / exposed	11 / 162 (6.79%)	12 / 164 (7.32%)	7 / 162 (4.32%)
occurrences (all)	14	13	7
Ear infection			
subjects affected / exposed	5 / 162 (3.09%)	10 / 164 (6.10%)	6 / 162 (3.70%)
occurrences (all)	9	11	12
Gastroenteritis			
subjects affected / exposed	12 / 162 (7.41%)	9 / 164 (5.49%)	4 / 162 (2.47%)
occurrences (all)	13	11	6
Nasopharyngitis			
subjects affected / exposed	23 / 162 (14.20%)	20 / 164 (12.20%)	13 / 162 (8.02%)
occurrences (all)	39	36	20
Otitis media			
subjects affected / exposed	56 / 162 (34.57%)	38 / 164 (23.17%)	37 / 162 (22.84%)
occurrences (all)	90	69	65
Otitis media acute			
subjects affected / exposed	14 / 162 (8.64%)	10 / 164 (6.10%)	12 / 162 (7.41%)
occurrences (all)	22	15	16
Pharyngitis			
subjects affected / exposed	18 / 162 (11.11%)	16 / 164 (9.76%)	12 / 162 (7.41%)
occurrences (all)	23	22	15
Pharyngitis streptococcal			
subjects affected / exposed	7 / 162 (4.32%)	7 / 164 (4.27%)	10 / 162 (6.17%)
occurrences (all)	9	8	12
Rhinitis			
subjects affected / exposed	14 / 162 (8.64%)	11 / 164 (6.71%)	13 / 162 (8.02%)
occurrences (all)	25	20	18
Sinusitis			

subjects affected / exposed	11 / 162 (6.79%)	16 / 164 (9.76%)	8 / 162 (4.94%)
occurrences (all)	13	19	9
Upper respiratory tract infection			
subjects affected / exposed	62 / 162 (38.27%)	54 / 164 (32.93%)	51 / 162 (31.48%)
occurrences (all)	99	100	82
Viral infection			
subjects affected / exposed	18 / 162 (11.11%)	14 / 164 (8.54%)	12 / 162 (7.41%)
occurrences (all)	21	19	15

Non-serious adverse events	15_(0)MF59		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 166 (85.54%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	39 / 166 (23.49%)		
occurrences (all)	53		
General disorders and administration site conditions			
Crying			
subjects affected / exposed	42 / 166 (25.30%)		
occurrences (all)	60		
Injection site pain			
subjects affected / exposed	50 / 166 (30.12%)		
occurrences (all)	76		
Pyrexia			
subjects affected / exposed	53 / 166 (31.93%)		
occurrences (all)	77		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	5 / 166 (3.01%)		
occurrences (all)	5		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	45 / 166 (27.11%)		
occurrences (all)	62		
Vomiting			
subjects affected / exposed	24 / 166 (14.46%)		
occurrences (all)	30		

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 166 (5.42%)		
occurrences (all)	18		
Bronchial Hyperreactivity			
subjects affected / exposed	7 / 166 (4.22%)		
occurrences (all)	9		
Cough			
subjects affected / exposed	54 / 166 (32.53%)		
occurrences (all)	73		
Nasal congestion			
subjects affected / exposed	11 / 166 (6.63%)		
occurrences (all)	12		
Rhinitis allergic			
subjects affected / exposed	3 / 166 (1.81%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	32 / 166 (19.28%)		
occurrences (all)	41		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	4 / 166 (2.41%)		
occurrences (all)	4		
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	23 / 166 (13.86%)		
occurrences (all)	32		
Irritability			
subjects affected / exposed	52 / 166 (31.33%)		
occurrences (all)	79		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	13 / 166 (7.83%)		
occurrences (all)	13		
Bronchitis			

subjects affected / exposed	7 / 166 (4.22%)			
occurrences (all)	7			
Conjunctivitis				
subjects affected / exposed	22 / 166 (13.25%)			
occurrences (all)	25			
Croup infectious				
subjects affected / exposed	12 / 166 (7.23%)			
occurrences (all)	15			
Ear infection				
subjects affected / exposed	8 / 166 (4.82%)			
occurrences (all)	16			
Gastroenteritis				
subjects affected / exposed	8 / 166 (4.82%)			
occurrences (all)	8			
Nasopharyngitis				
subjects affected / exposed	20 / 166 (12.05%)			
occurrences (all)	30			
Otitis media				
subjects affected / exposed	45 / 166 (27.11%)			
occurrences (all)	75			
Otitis media acute				
subjects affected / exposed	12 / 166 (7.23%)			
occurrences (all)	23			
Pharyngitis				
subjects affected / exposed	17 / 166 (10.24%)			
occurrences (all)	21			
Pharyngitis streptococcal				
subjects affected / exposed	5 / 166 (3.01%)			
occurrences (all)	5			
Rhinitis				
subjects affected / exposed	13 / 166 (7.83%)			
occurrences (all)	19			
Sinusitis				
subjects affected / exposed	13 / 166 (7.83%)			
occurrences (all)	15			
Upper respiratory tract infection				

subjects affected / exposed	64 / 166 (38.55%)		
occurrences (all)	95		
Viral infection			
subjects affected / exposed	17 / 166 (10.24%)		
occurrences (all)	23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2009	- Solicited local injection site reactions will be evaluated using CBER toxicity scales and solicited systemic reactions will be evaluated using a standardized severity scale employed in other Novartis Vaccines and Diagnostics studies in children in this age range. The previous version of the protocol included the DAIDS toxicity tables for use of solicited local and systemic reactions. - Types of solicited local reactions changed from: erythema, induration, edema, pruritus, and injection site tenderness to erythema, ecchymosis, induration, swelling, and tenderness at injection site. Types of solicited systemic reactions changed from: acute systemic allergic reaction, body pain, fatigue, malaise, chills, arthralgia, vomiting, diarrhea, and anorexia to sleepiness, diarrhea, vomiting, irritability, change in eating habits, persistent crying, and fever - Preferred route of body temperature measurement switched from oral measurement to rectal as the preferred route with axillary measurement as the back-up. -. Adjusted serious adverse events reporting to include subjects with confirmed "potentially life threatening" graded local and systemic reactions and laboratory abnormalities
03 February 2010	Added the secondary objective: To evaluate antibody persistence at 6 and 12 months post last study vaccination to evaluate immunogenicity against drifted strains (cross protection) and antibody persistence.
08 February 2010	- Increased visit windows for Visit 10 and Visit 16 additional blood draws to -7/+14 days - References to 6 and 12 months post-vaccination were replaced by day 202 and day 387 to be consistent with the inclusion of subjects receiving only one vaccination for optional blood draws at Visit 10 (Day 202) and Visit 16 (Day 387).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported