Clinical trial results:
A Phase 3, Open-Label, Randomized, Multi-Center Study to Evaluate the Safety and Immunogenicity of ProQuad™ Vaccine When Administered Concomitantly with Novartis Meningococcal ACWY Conjugate Vaccine to Healthy Toddlers.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2014-004694-16
Trial protocol	Outside EU/EEA
Global end of trial date	26 October 2010

Results information

Result version number	v2 (current)
This version publication date	01 June 2016
First version publication date	06 February 2015
Version creation reason	• Correction of full data set re-QC study because of EudraCT system glitch and updates to results are required.

Trial information

Trial identification

Sponsor protocol code	V59P21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00626327
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics Inc.
Sponsor organisation address	350 Massachusetts Ave, Cambridge, United States, 02139
Public contact	Posting Director, Novartis Vaccines and Diagnostics Inc., RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics Inc., 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-000032-PIP01-07
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	11 February 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 October 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To compare the immune responses of ProQuad™ vaccine when administered with MenACWY vaccine to that of ProQuad™ vaccine alone to children 12 months of age, as measured by seroconversion rates to measles, mumps, and rubella, and seroprotection rates for varicella.
- To compare the immune responses of two doses of MenACWY given to children at 7 to 9 and 12 months of age, when either administered with ProQuad™ or given alone, as measured by percentage of subjects with serum bactericidal activity (hSBA) ≥1:8 against N. meningitidis serogroups A, C, W-135, and Y.
- To assess the immunogenicity of two doses of MenACWY given to children at 7 to 9 and 12 months of age as measured by the percentage of subjects with hSBA ≥1:8 against N. meningitidis serogroups A, C, W-135, and Y.

Protection of trial subjects:

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

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	27 February 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 1630
Worldwide total number of subjects	1630
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)	1630
Children (2-11 years)	0
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:

Subjects were enrolled at 90 sites in US.

Pre-assignment

Screening details:

All enrolled subjects 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	Not blinded

Blinding implementation details:

The trial was designed as an open-label study; both the study personnel and the subjects' parents/legal guardians knew which vaccine was being administered. However, laboratory immunogenicity analyses were conducted in a blinded fashion with samples blinded to both group and visit.

Arms

Are arms mutually exclusive?	Yes
Arm title	ACWY + MMRV

Arm description:

Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.

Arm type	Experimental
Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	Measles, Mumps, Rubella and Varicella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One dose of 0.5mL

Investigational medicinal product name	MenACWY
Investigational medicinal product code	
Other name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses of 0.5mL each

Arm title	ACWY

Arm description:

Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months.

Arm type	Experimental
Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	Measles, Mumps, Rubella and Varicella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details: One dose of 0.5mL	
Investigational medicinal product name	MenACWY
Investigational medicinal product code	
Other name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: Two doses of 0.5mL each	
Arm title	MMRV
Arm description: Subjects in this group received 1 injection of MMRV vaccine at 12 months of age.	
Arm type	Experimental
Investigational medicinal product name	ProQuad™
Investigational medicinal product code	
Other name	Measles, Mumps, Rubella and Varicella vaccine
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: One dose of 0.5mL	

Number of subjects in period 1	ACWY + MMRV	ACWY	MMRV
Started	504	510	616
Completed	426	422	557
Not completed	78	88	59
Consent withdrawn by subject	21	30	29
Adverse event, non-fatal	1	-	-
Inappropriate enrolment	4	3	5
Lost to follow-up	24	23	21
Administrative reason	2	6	-
Protocol deviation	26	26	4

Baseline characteristics

Reporting groups	
Reporting group title	ACWY + MMRV
Reporting group description:	
Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.	
Reporting group title	ACWY
Reporting group description:	
Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months.	
Reporting group title	MMRV
Reporting group description:	
Subjects in this group received 1 injection of MMRV vaccine at 12 months of age.	

Reporting group values	ACWY + MMRV	ACWY	MMRV
Number of subjects	504	510	616
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	8.5	8.5	12.1
standard deviation	± 0.8	± 0.8	± 0.3
Gender categorical Units: Subjects			
Female	251	252	304
Male	253	258	312

Reporting group values	Total		
Number of subjects	1630		
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	807		
Male	823		

Subject analysis sets	
Subject analysis set title	Exposed Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled subjects who actually received a study vaccination.	

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

Subject analysis set description:

All subjects who signed an informed consent, undergone screening procedure and were randomized (Groups I and II only) or enrolled (Group III).

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

Subject analysis set description:

All subjects who actually received one study vaccination correctly, provided evaluable serum samples at the relevant time points, were seronegative at baseline for any of the four antigens (MMRV analyses only), were included in the analysis of those antigens, and had no major protocol deviation as defined prior to unblinding. These subjects would have received either ProQuad™ or M-M-R™II + Varivax™.

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

Subject analysis set description:

All subjects who actually received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, were included in the analysis of that antigen, and had no major protocol deviation as defined prior to unblinding.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

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

Reporting group values	Exposed Population	Enrolled Population	MMRV Per Protocol Population (PP - MMRV)
Number of subjects	1603	1630	1318
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	±	9.8 ± 1.9	±
Gender categorical Units: Subjects			
Female		807	
Male		823	

Reporting group values	MenACWY Per Protocol Population (PP - MenACWY)	Safety Population	
Number of subjects	1319	1597	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	ACWY + MMRV
Reporting group description:	
Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.	
Reporting group title	ACWY
Reporting group description:	
Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months.	
Reporting group title	MMRV
Reporting group description:	
Subjects in this group received 1 injection of MMRV vaccine at 12 months of age.	
Subject analysis set title	Exposed Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled subjects who actually received a study vaccination.	
Subject analysis set title	Enrolled Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who signed an informed consent, undergone screening procedure and were randomized (Groups I and II only) or enrolled (Group III).	
Subject analysis set title	MMRV Per Protocol Population (PP - MMRV)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who actually received one study vaccination correctly, provided evaluable serum samples at the relevant time points, were seronegative at baseline for any of the four antigens (MMRV analyses only), were included in the analysis of those antigens, and had no major protocol deviation as defined prior to unblinding. These subjects would have received either ProQuad™ or M-M-R™II + Varivax™.	
Subject analysis set title	MenACWY Per Protocol Population (PP - MenACWY)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who actually received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, were included in the analysis of that antigen, and had no major protocol deviation as defined prior to unblinding.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Population who provided post-baseline safety data.	

Primary: 1. Percentages of Subjects With a Seroresponse to Measles, Mumps, Rubella and Varicella Following Concomitant Administration of MMRV Vaccine With MenACWY Vaccine

End point title	1. Percentages of Subjects With a Seroresponse to Measles, Mumps, Rubella and Varicella Following Concomitant Administration of MMRV Vaccine With MenACWY Vaccine[1]
End point description:	
Percentages of subjects with seroresponses to measles, mumps, rubella and varicella after one dose of MMRV vaccine (at 12 months) when given concomitantly with MenACWY vaccine compared to when MMRV vaccine was given alone, are reported. Seroresponse was defined as the percentage of initially seronegative subjects who show seroconversion to measles (≥255 mIU/mL), mumps (≥10 ELISA Ab units), rubella (≥10 IU/mL) and varicella (≥5 gp ELISA units/mL). Immunogenicity to measles, mumps, rubella and varicella at 6 weeks after vaccination with one dose of MMRV given concomitantly with MenACWY was considered non-inferior to immunogenicity of MMRV administered alone if the lower limit of two-sided 95% CI of the difference in	

the percentage of subjects with seroconversion for measles, mumps, and rubella was greater than -5%, and seroprotection for varicella was greater than -10%.
The analysis was performed on the MMRV Per Protocol Population.

End point type	Primary

End point timeframe:

6 weeks post vaccination

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	MMRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370	515		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Measles (N=350,467)	98 (96 to 99)	99 (98 to 100)		
Mumps (N=365,499)	98 (96 to 99)	96 (94 to 98)		
Rubella (370,515)	95 (93 to 97)	97 (95 to 98)		
Varicella (N=337,459)	96 (94 to 98)	98 (96 to 99)		

Statistical analyses

Statistical analysis title	Non-inferiority of immune response to measles

Statistical analysis description:

Non-inferiority of immune response to measles following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for measles was greater than -5%, at 6 weeks after MMRV vaccination.

Comparison groups	ACWY + MMRV v MMRV
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.5

Statistical analysis title	Non-inferiority of immune response to mumps

Statistical analysis description:

Non-inferiority of immune response to mumps following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for mumps was greater than -5%, at 6

weeks after MMRV vaccination.

Comparison groups	ACWY + MMRV v MMRV
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3.7

Statistical analysis title	Non-inferiority of immune response to rubella

Statistical analysis description:

Non-inferiority of immune response to rubella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for rubella was greater than -5%, at 6 weeks after MMRV vaccination.

Comparison groups	ACWY + MMRV v MMRV
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	0.8

Statistical analysis title	Non-inferiority of immune response to varicella

Statistical analysis description:

Non-inferiority of immune response to varicella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for varicella was greater than -10%, at 6 weeks after MMRV vaccination.

Comparison groups	ACWY + MMRV v MMRV
Number of subjects included in analysis	885
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	-1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	1.2

Primary: 2. Percentages of Subjects With Serum Bactericidal Titers ≥1:8 Following Concomitant Administration of MenACWY Vaccine With MMRV Vaccine.

End point title	2. Percentages of Subjects With Serum Bactericidal Titers ≥1:8 Following Concomitant Administration of MenACWY Vaccine With MMRV Vaccine.[2]

End point description:

Percentages of subjects with hSBA ≥1:8, against N.meningitidis serogroups A, C, W-135, and Y following two doses of MenACWY vaccine (at 7-9 months and 12 months) when concomitantly administered with MMRV vaccine (12 months) compared to when MenACWY vaccine was given alone, are reported.
The serum bactericidal antibodies directed against N.meningitidis serogroups A, C, W-135, and Y, were measured by human complement Serum Bactericidal Assay (hSBA). The immune response of MenACWY given concomitantly with MMRV was considered non-inferior to the immunogenicity of MenACWY administered alone if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY given to 12-month old toddlers {P MMRV+MenACWY minus P MenACWY} was greater than -10% for each serogroup.
The analysis was performed on the MenACWY Per Protocol population.

End point type	Primary

End point timeframe:

6 weeks post vaccination

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	ACWY		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	379		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A	88 (84 to 91)	88 (84 to 91)		
Serogroup C (N=204,195)	100 (98 to 100)	100 (98 to 100)		
Serogroup W-135 (N=204,196)	100 (97 to 100)	98 (96 to 100)		
Serogroup Y (N=200,198)	98 (95 to 99)	96 (93 to 99)		

Statistical analyses

Statistical analysis title	non-inferiority against serogroup A

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup A when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.
The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater

than -10% for each serogroup.

Comparison groups	ACWY + MMRV v ACWY
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	4.5

Statistical analysis title	non-inferiority against serogroup C

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup C when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.
The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

Comparison groups	ACWY + MMRV v ACWY
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.9

Statistical analysis title	non-inferiority against serogroup W-135

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup W-135 when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.
The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

Comparison groups	ACWY + MMRV v ACWY

Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	3.9

Statistical analysis title	non-inferiority against serogroup Y

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup Y when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.
The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

Comparison groups	ACWY + MMRV v ACWY
Number of subjects included in analysis	763
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	5.3

Primary: 3. Percentages of Subjects With hSBA ≥1:8 Following Two Doses of MenACWY Vaccine

End point title	3. Percentages of Subjects With hSBA ≥1:8 Following Two Doses of MenACWY Vaccine[3][4]

End point description:

The antibody response following two doses of MenACWY vaccine (at 7-9 months and 12 months) was considered adequate if the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 6 weeks following the second dose of MenACWY, was greater than 85% for serogroups C, W-135, or Y and greater than 65% for serogroup A. The analysis was performed on the MenACWY Per Protocol population.

End point type	Primary

End point timeframe:

6 weeks post second vaccination dose

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: There was no statistical null hypothesis associated with this immunogenicity objective.

[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: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY			
Subject group type	Reporting group			
Number of subjects analysed	379			
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A	88 (84 to 91)			
Serogroup C (N=195)	100 (98 to 100)			
Serogroup W-135 (N=196)	98 (96 to 100)			
Serogroup Y (N=198)	96 (93 to 99)			

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Percentages of Subjects With hSBA ≥1:4 Following Two Doses of MenACWY Vaccine

End point title	4. Percentages of Subjects With hSBA ≥1:4 Following Two Doses of MenACWY Vaccine[5]

End point description:

The percentages of subjects with hSBA ≥1:4 directed against N. meningitidis serogroups A, C, W-135, and Y following two doses of MenACWY vaccine (at 7- 9 and 12 months of age) when given concomitantly with MMRV vaccine (at 12 months) compared to when MenACWY vaccine was given alone, are reported.
The analysis was performed on the MenACWY Per Protocol population.

End point type	Secondary

End point timeframe:

6 weeks post second vaccination dose

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	ACWY		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	379		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A	90 (86 to 92)	91 (87 to 93)		
Serogroup C (N=204,195)	100 (98 to 100)	100 (98 to 100)		
Serogroup W-135 (N=204,196)	100 (97 to 100)	99 (96 to 100)		
Serogroup Y (N=200,198)	98 (95 to 99)	98 (95 to 99)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Geometric Mean Titers Against Serogroups A, C, W-135 and Y, Following Two Doses of MenACWY Vaccine

End point title	5. Geometric Mean Titers Against Serogroups A, C, W-135 and Y, Following Two Doses of MenACWY Vaccine[6]

End point description:

The geometric mean titers (GMTs) directed against N. meningitidis serogroups A, C, W-135 and Y, following two doses of MenACWY vaccine (at 7-9 months and 12 months of age), when given concomitantly with MMRV vaccine (at 12 months) compared to when MenACWY vaccine was given alone, are reported.
The analysis was performed on the MenACWY Per Protocol population.

End point type	Secondary

End point timeframe:

6 weeks post second vaccination dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	ACWY		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	384	379		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A	39 (34 to 45)	37 (32 to 42)		
Serogroup C (N=204,195)	194 (170 to 220)	180 (158 to 205)		
Serogroup W-135 (N=204,196)	132 (113 to 155)	119 (101 to 139)		
Serogroup Y (N=200,198)	97 (81 to 116)	88 (73 to 105)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Geometric Mean Titers Against Measles, Mumps, Rubella and Varicella Following One Dose of MMRV Vaccine

End point title	6. Geometric Mean Titers Against Measles, Mumps, Rubella and Varicella Following One Dose of MMRV Vaccine[7]

End point description:

The GMTs directed against measles, mumps, rubella and varicella, following one dose of MMRV vaccine (at 12 months) when given concomitantly with MenACWY vaccine compared to when MMRV vaccine was given alone, are reported.
The analysis was performed on the MMRV Per Protocol population.

End point type	Secondary

End point timeframe:

6 weeks post vaccination

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	MMRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	377	518		
Units: Titers				
geometric mean (confidence interval 95%)				
Pre-dose, Measles (N=357,470)	74 (71 to 77)	74 (71 to 77)		
Post-dose, Measles (N=350,467)	4049 (3701 to 4430)	3632 (3350 to 3938)		
Pre-dose, Mumps (N=372,502)	5 (5 to 5)	5 (5 to 5)		
Post-dose, Mumps (N=365,499)	97 (89 to 107)	81 (75 to 88)		
Pre-dose, Rubella	5 (5 to 5)	5 (5 to 5)		
Post-dose, Rubella (370,515)	57 (52 to 62)	56 (52 to 61)		
Pre-dose, Varicella (N=344,461)	0.63 (0.63 to 0.63)	0.63 (0.63 to 0.63)		
Post-dose, Varicella (N=337,459)	19 (17 to 20)	18 (17 to 19)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Percentages of Subjects Showing Seroconversion Response to Varicella Following Concomitant Administration of MMRV With MenACWY Vaccine

End point title	7. Percentages of Subjects Showing Seroconversion Response to Varicella Following Concomitant Administration of MMRV With MenACWY Vaccine[8]

End point description:

The percentages of subjects showing seroconversion response to varicella after concomitant administration of MMRV vaccine (at 12 months) with MenACWY vaccine compared to when MMRV vaccine is given alone, is reported.
Seroconversion for varicella is defined as the percentage of subjects who show pre-vaccination antibody titer <1.25 gp ELISA units/mL to a post-vaccination antibody titer ≥1.25 gp ELISA units/mL.
The analysis was performed on the MMRV Per Protocol population.

End point type	Secondary

End point timeframe:

6 weeks post vaccination

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY + MMRV	MMRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	459		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Varicella	99 (97 to 100)	99 (98 to 100)		

Statistical analyses

Statistical analysis title	Non-inferiority of immune response to varicella

Statistical analysis description:

Non-inferiority of immune response to varicella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of ACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for varicella was greater than -10%, at 6 weeks after MMRV vaccination.

Comparison groups	ACWY + MMRV v MMRV
Number of subjects included in analysis	796
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	95% Confidence Intervals
Parameter estimate	Percentage group difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	0.8

Secondary: 8. Percentages of Subjects With hSBA ≥1:4 and hSBA ≥1:8 Following One Dose of MenACWY Vaccine

End point title	8. Percentages of Subjects With hSBA ≥1:4 and hSBA ≥1:8 Following One Dose of MenACWY Vaccine[9]

End point description:

The percentages of subjects with hSBA ≥1:4 and hSBA ≥1:8 after one dose of MenACWY vaccine (at 7-9 months), are reported.
The analysis was performed on the MenACWY Per Protocol population.

End point type	Secondary

End point timeframe:

1 month post first vaccination dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A hSBA ≥1:4	63 (57 to 68)			
Serogroup A hSBA ≥1:8	50 (45 to 56)			

Serogroup C (N=199) hSBA ≥1:4	93 (88 to 96)			
Serogroup C (N=199) hSBA ≥1:8	88 (83 to 92)			
Serogroup W-135 (N=199) hSBA ≥1:4	48 (41 to 55)			
Serogroup W-135 (N=199) hSBA ≥1:8	37 (30 to 44)			
Serogroup Y (N=196) hSBA ≥1:4	41 (34 to 49)			
Serogroup Y (N=196) hSBA ≥1:8	31 (24 to 38)			

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Geometric Mean Titers After One Dose of MenACWY Vaccine

End point title	9. Geometric Mean Titers After One Dose of MenACWY

End point description:

The immunogenicity of one dose of MenACWY vaccine given at 7 to 9 months of age was assessed in terms of GMTs directed against N.meningitidis serogroups A, C, W-135, and Y.
The analysis was performed on the MenACWY Per Protocol population.

End point type	Secondary

End point timeframe:

1 month post first vaccination dose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

End point values	ACWY			
Subject group type	Reporting group			
Number of subjects analysed	349			
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A	8.16 (6.96 to 9.58)			
Serogroup C (N=199)	26 (22 to 31)			
Serogroup W-135 (N=199)	5.11 (4.15 to 6.29)			
Serogroup Y (N=196)	4.09 (3.36 to 4.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Number of Subjects Reporting Solicited Local and Systemic Adverse Events After Any Vaccination

End point title	10. Number of Subjects Reporting Solicited Local and Systemic Adverse Events After Any Vaccination

End point description:

Safety and tolerability of MenACWY and MMRV vaccines when given concomitantly compared to when either MenACWY or MMRV vaccine was administered alone is reported in terms of the number of subjects with local and systemic adverse events after any vaccination.
Systemic reactions including axillary temperature with onset during the first 7 days after any study vaccination were reported. These included the following systemic reactions: Measles-like rash, Rubella-like rash, Varicella-like rash, injection site rash, Mumps-like symptoms and axillary temperature.
The analysis was done on the safety population.

End point type	Secondary

End point timeframe:

Up to 7 days after each study vaccine injection.

End point values	ACWY + MMRV	ACWY	MMRV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500	500	597	
Units: Subjects				
Any Local	278	298	316	
Injection (Inj.) site Tenderness [MenACWY]	133	129	0	
Inj. site Erythema [MenACWY]	153	159	0	
Inj. site Induration [MenACWY]	74	74	0	
Inj. site Tenderness [MMRV (N=455,424,592)]	105	102	179	
Inj. site Erythema [MMRV (N=456,425,593)]	156	145	224	
Inj. site Induration [MMRV (456,424,593)]	90	60	102	
Any Systemic Reaction	371	372	381	
Rash (N=500,499,595)	54	44	46	
Change in eating habits (N=475,483,550)	132	136	105	
Sleepiness (N=500,499,595)	219	199	197	
Persistent crying (N=475,483,550)	135	152	109	
Irritability (N=500,500,595)	273	298	298	
Vomiting (N=500,499,595)	66	74	36	
Diarrhea (N=500,499,595)	120	123	107	
Fever (≥ 38C) (N=499,500,596)	58	78	42	
Analgesic Antipyr. Meds (N=499,499,594)	208	254	203	

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Number of Subjects Reporting Unsolicited Adverse Events After Vaccination

End point title	11. Number of Subjects Reporting Unsolicited Adverse Events After Vaccination

End point description:

The safety profile of MenACWY and MMRV vaccines when given concomitantly as compared to when

MenACWY or MMRV was given alone is reported in terms of number of subjects reporting unsolicited adverse events (AEs), medically significant adverse events and serious adverse events (SAEs) after vaccination.
The analysis was done on the safety population.

End point type	Secondary

End point timeframe:

Day 1- Day 180 (Throughout the study)

End point values	ACWY + MMRV	ACWY	MMRV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	500	500	597	
Units: Subjects				
Any AEs	335	353	311	
At least possibly related AEs	70	63	2	
Serious AEs	18	19	9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited adverse events (AEs) were collected up to Day 7 after each vaccination.
All SAEs and unsolicited AEs were collected throughout the study (Day 1-Day 180).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	ACWY + MMRV

Reporting group description:

Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.

Reporting group title	MMRV

Reporting group description:

Subjects in this group received 1 injection of MMRV vaccine at 12 months of age.

Reporting group title	ACWY

Reporting group description:

Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months

Serious adverse events	ACWY + MMRV	MMRV	ACWY
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 500 (3.60%)	9 / 597 (1.51%)	19 / 500 (3.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Hand fracture			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			

subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Tethered cord syndrome			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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			
Apnoea			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			

subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Bronchial hyperreactivity			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Respiratory distress			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Tachypnoea			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Wheezing			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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			
Arthritis bacterial			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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	1 / 500 (0.20%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Croup infectious			
subjects affected / exposed	1 / 500 (0.20%)	2 / 597 (0.34%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Gastroenteritis			
subjects affected / exposed	2 / 500 (0.40%)	0 / 597 (0.00%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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 viral			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Lobar pneumonia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Pneumococcal sepsis			

subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	1 / 500 (0.20%)
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 respiratory syncytial viral			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Postoperative wound infection			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 500 (0.20%)	2 / 597 (0.34%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			

subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Staphylococcal infection			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	2 / 500 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Toxic shock syndrome			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 500 (0.00%)	1 / 597 (0.17%)	0 / 500 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	3 / 500 (0.60%)	1 / 597 (0.17%)	3 / 500 (0.60%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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
Feeding disorder			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 500 (0.00%)	0 / 597 (0.00%)	1 / 500 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 500 (0.20%)	0 / 597 (0.00%)	0 / 500 (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

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

Non-serious adverse events	ACWY + MMRV	MMRV	ACWY
Total subjects affected by non-serious adverse events			
subjects affected / exposed	433 / 500 (86.60%)	482 / 597 (80.74%)	442 / 500 (88.40%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	219 / 500 (43.80%)	197 / 597 (33.00%)	199 / 500 (39.80%)
occurrences (all)	424	290	443
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	219 / 500 (43.80%)	224 / 597 (37.52%)	230 / 500 (46.00%)
occurrences (all)	484	263	466
Injection site pain			

subjects affected / exposed	163 / 500 (32.60%)	180 / 597 (30.15%)	188 / 500 (37.60%)
occurrences (all)	345	233	318
Injection site induration			
subjects affected / exposed	128 / 500 (25.60%)	102 / 597 (17.09%)	115 / 500 (23.00%)
occurrences (all)	254	130	221
Pyrexia			
subjects affected / exposed	90 / 500 (18.00%)	70 / 597 (11.73%)	114 / 500 (22.80%)
occurrences (all)	116	84	160
Crying			
subjects affected / exposed	135 / 500 (27.00%)	109 / 597 (18.26%)	152 / 500 (30.40%)
occurrences (all)	261	161	312
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	125 / 500 (25.00%)	114 / 597 (19.10%)	128 / 500 (25.60%)
occurrences (all)	220	185	255
Teething			
subjects affected / exposed	41 / 500 (8.20%)	41 / 597 (6.87%)	60 / 500 (12.00%)
occurrences (all)	51	48	73
Vomiting			
subjects affected / exposed	68 / 500 (13.60%)	43 / 597 (7.20%)	79 / 500 (15.80%)
occurrences (all)	113	60	123
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	26 / 500 (5.20%)	29 / 597 (4.86%)	30 / 500 (6.00%)
occurrences (all)	29	29	34
Rash			
subjects affected / exposed	76 / 500 (15.20%)	87 / 597 (14.57%)	52 / 500 (10.40%)
occurrences (all)	128	135	102
Psychiatric disorders			
Irritability			
subjects affected / exposed	273 / 500 (54.60%)	299 / 597 (50.08%)	299 / 500 (59.80%)
occurrences (all)	654	481	788
Eating disorder			
subjects affected / exposed	132 / 500 (26.40%)	105 / 597 (17.59%)	136 / 500 (27.20%)
occurrences (all)	260	166	292
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	71 / 500 (14.20%)	20 / 597 (3.35%)	92 / 500 (18.40%)
occurrences (all)	86	22	110
Otitis media			
subjects affected / exposed	92 / 500 (18.40%)	40 / 597 (6.70%)	120 / 500 (24.00%)
occurrences (all)	126	42	160

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2007	Substantial changes: to add requested new primary immunogenicity objective; to update the immunogenicity criteria to incorporate the new third co-primary objective; to add the null hypothesis for the two-dose immunogenicity; to add statistical power computations for the two-dose MenACWY objective; to clarify SAE reporting; to clarify major deviations and demographic data analysis; to update analysis of immunogenicity criteria for new co-primary objective.
02 October 2008	Clarifications on study procedures and terms.
17 February 2009	Due to a shortage of ProQuad on the US market, for subjects enrolled into the trial in Groups 1 and 2, M-M-R II and Varivax to be administered in place of ProQuad.
28 May 2009	Statistical and operational changes to allow for use of M-M-R® II and Varivax® instead of ProQuad.
04 March 2010	To allow for use of frozen ProQuad and change storage temperatures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 January 2009	Due to shortage of ProQuad.	03 July 2009

Notes:

Limitations and caveats

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

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22504039