Clinical trial results:
A Phase 3, randomized, open label, controlled multi center study to evaluate the safety and immunogenicity of 4 doses of MenACWY conjugate vaccine, administered concomitantly with routine vaccines, among infants aged 2 months

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

Summary

EudraCT number	2014-005061-72
Trial protocol	Outside EU/EEA
Global end of trial date	23 November 2011

Results information

Result version number	v2 (current)
This version publication date	04 June 2016
First version publication date	04 April 2015
Version creation reason	• Correction of full data set re-QC study needed because of EuddraCT system glitch and updates to results required.

Trial information

Trial identification

Sponsor protocol code	V59_33

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01000311
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics
Sponsor organisation address	350 Massachusetts Avenue, Cambridge, United States, 02139
Public contact	Posting Director, Novartis Vaccine, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccine, 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	09 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants in terms of the percentages of subjects with an human Serum Bacteridal Assay (hSBA) ≥1:8 at 1 month post vaccination, for each of the four meningococcal vaccine serogroups.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 74
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 449
Worldwide total number of subjects	529
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	529

months)	
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 from 42 sites in USA, 3 sites in Australia and 1 site in Canada

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 subject's parent/legal guardian knew the vaccines being administered; however, randomization was done in a blinded manner. Laboratory staff were blinded to the study group allocation when processing the serologies.

Arms

Are arms mutually exclusive?	Yes
Arm title	MenACWY-CRM + Routine Vaccines

Arm description:

Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

Arm type	Experimental
Investigational medicinal product name	Meningococcal Group A, C, W135 and Y conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One 0.5 mL dose of MenACWY was administered by intramuscular injection in the anterolateral area of the thigh.

Investigational medicinal product name	Pentacel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

Investigational medicinal product name	Prevnar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

Investigational medicinal product name	HBV vaccine
Investigational medicinal product code	
Other name	Hepatitis B vaccine, Engerix-B, H-B-VAX II, RECOMBINAX, Pediarix

Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

Investigational medicinal product name	MMR
Investigational medicinal product code	
Other name	MEASLES, MUMPS, and RUBELLA VIRUS VACCINE
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

Arm title	Routine Vaccines

Arm description:

Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

Arm type	Active comparator
Investigational medicinal product name	Pentacel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

Investigational medicinal product name	HBV vaccine
Investigational medicinal product code	
Other name	Hepatitis B vaccine, Engerix-B, H-B-VAX II, RECOMBINAX
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

Investigational medicinal product name	Prevnar
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

Investigational medicinal product name	MMR
Investigational medicinal product code	
Other name	MEASLES, MUMPS, and RUBELLA VIRUS VACCINE
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

Number of subjects in period 1	MenACWY-CRM + Routine Vaccines	Routine Vaccines
Started	258	271
Completed	213	201
Not completed	45	70
Consent withdrawn by subject	16	24
Inappropriate enrollment	2	-
Adverse event	2	5
Lost to follow-up	15	24
Administrative reason	9	15
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	MenACWY-CRM + Routine Vaccines
Reporting group description:	
Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	
Reporting group title	Routine Vaccines
Reporting group description:	
Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	

Reporting group values	MenACWY-CRM + Routine Vaccines	Routine Vaccines	Total
Number of subjects	258	271	529
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: days			
arithmetic mean	64.7	65.4	
standard deviation	± 6.5	± 7.4	-
Gender categorical Units: Subjects			
Female	125	130	255
Male	133	141	274

End points

End points reporting groups

Reporting group title	MenACWY-CRM + Routine Vaccines
Reporting group description:	
Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	
Reporting group title	Routine Vaccines
Reporting group description:	
Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who have signed an informed consent, undergone screening procedures, and are randomized	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the exposed population who provide post-baseline safety data.	
Subject analysis set title	Exposed Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who actually receive a study vaccination.	
Subject analysis set title	Per Protocol - Concomitant Infant
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.	
Subject analysis set title	Per Protocol - Pertussis Infant
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.	
Subject analysis set title	Per Protocol - Hepatitis B Infant
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.	
Subject analysis set title	Per Protocol - MenACWY Infant
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.	
Subject analysis set title	Per Protocol - Pneumococcal Toddler
Subject analysis set type	Per protocol
Subject analysis set description:	
All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.	
Subject analysis set title	Per Protocol - MenACWY Toddler
Subject analysis set type	Per protocol

Subject analysis set description:

All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.

Primary: 1. Percentage of Subjects With human Serum Bactericidal Assay (hSBA) Titer ≥1:8 Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point title	1. Percentage of Subjects With human Serum Bactericidal Assay (hSBA) Titer ≥1:8 Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point description:

Immunogenicity was measured as the percentage of subjects who achieved hSBA titer ≥1:8 against meningococcal serogroup A, C, W and Y, evaluated by serum bactericidal assay using human complement, at baseline and one month after toddler vaccination administered at 12 months of age. The immune response was considered sufficient if the lower limit of the two-sided 95% confidence intervals (CIs) for the percentage of subjects with hSBA titer ≥1:8, at one month after toddler vaccination, was greater than 85% for the serogroup C, W, or Y and greater than 80% for the serogroup A.
Analysis was done on the per-protocol (PP) toddler dataset for MenACWY-CRM.

End point type	Primary

End point timeframe:

Baseline and one month after toddler dose (month 13).

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	178		
Units: percentage of subjects				
number (confidence interval 95%)				
Serogroup A - Baseline (N=170,178)	7 (4 to 12)	2 (0 to 5)		
Serogroup A - Post-4th dose (N=168,175)	89 (83 to 93)	2 (0 to 5)		
Serogroup C - Baseline (N=166,174)	37 (30 to 45)	2 (1 to 6)		
Serogroup C - Post-4th dose (N=156,171)	95 (90 to 98)	2 (1 to 6)		
Serogroup W - Baseline (N=152,164)	70 (62 to 77)	5 (2 to 9)		
Serogroup W - Post-4th dose (N=153,165)	97 (93 to 99)	7 (3 to 12)		
Serogroup Y - Baseline (N=144,150)	53 (45 to 61)	3 (1 to 6)		
Serogroup Y - Post-4th dose (N=153,159)	96 (92 to 99)	1 (0 to 4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA ≥1:8 against serogroup A at 1 month post 4th vaccination.

Comparison groups	Routine Vaccines v MenACWY-CRM + Routine Vaccines

Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	lower limit of the two-sided 95% CI
Point estimate	89
Confidence interval	
level	95 %
sides	2-sided
lower limit	83
upper limit	93

Notes:

[1] - Success criterion:
The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 1 month after the fourth dose, to be greater than 80% for serogroup A.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA ≥1:8 against serogroup C at 1 month post 4th vaccination.

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	lower limit of the two-sided 95% CI
Point estimate	95
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	98

Notes:

[2] - Success criterion:
The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 1 month after the fourth dose, to be greater than 85% for serogroup C.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA ≥1:8 against serogroup W at 1 month post 4th vaccination.

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	lower limit of the two-sided 95% CI
Point estimate	97
Confidence interval	
level	95 %
sides	2-sided
lower limit	93
upper limit	99

Notes:

[3] - Success criterion:
The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 1 month after the fourth dose, to be greater than 85% for serogroup W.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA ≥1:8 against serogroup Y at 1 month post 4th vaccination.

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	lower limit of the two-sided 95% CI
Point estimate	96
Confidence interval	
level	95 %
sides	2-sided
lower limit	92
upper limit	99

Notes:

[4] - Success criterion:
The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA ≥1:8, at 1 month after the fourth dose, to be greater than 85% for serogroup Y.

Secondary: 2.hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point title	2.hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point description:

Immunogenicity was measured as the hSBA GMTs directed against meningococcal serogroup A, C, W and Y, at baseline and one month after toddler vaccination administered at 12 months of age. Analysis was performed on the PP toddler dataset for MenACWY-CRM vaccination

End point type	Secondary

End point timeframe:

Baseline and one month after toddler vaccination (month 13)

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	175		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A - Baseline (N=139,145)	2.07 (1.98 to 2.16)	2.01 (1.99 to 2.03)		
Serogroup A - Post-4th dose (N=168,175)	54 (44 to 67)	1.87 (1.55 to 2.27)		
Serogroup C - Baseline (N=126,136)	2.49 (2.2 to 2.83)	2.44 (2.2 to 2.7)		

Serogroup C - Post-4th dose (N=156,171)	135 (107 to 171)	1.94 (1.56 to 2.4)		
Serogroup W - Baseline (N=113,126)	2.99 (2.49 to 3.6)	2.97 (2.52 to 3.51)		
Serogroup W - Post-4th dose (N=153,165)	215 (167 to 277)	2.15 (1.77 to 2.6)		
Serogroup Y - Baseline (N=108,113)	2.43 (2.19 to 2.71)	2.32 (2.13 to 2.52)		
Serogroup Y - Post-4th dose (N=153,159)	185 (148 to 233)	1.89 (1.56 to 2.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3. Percentage of Subjects With hSBA Titers ≥1:8 and Four-Fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

End point title	3. Percentage of Subjects With hSBA Titers ≥1:8 and Four-Fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

End point description:

Immunogenicity was measured as the percentage of subjects with hSBA titers ≥1:8 against meningococcal serogroup A, C, W and Y, at baseline and one month after three infant doses of vaccines administered at 2, 4 and 6 months of age.
Percentage of subjects who achieved at least four-fold rise in hSBA titers against serogroup A, C, W and Y was measured one month after three doses of infant series vaccination.
Analysis was performed on the PP dataset of MenACWY-CRM infant vaccination series.

End point type	Secondary

End point timeframe:

Baseline and one month after three doses of infant vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	208		
Units: Percentage of subjects				
number (confidence interval 95%)				
Serogroup A - hSBA ≥1:8-Baseline (N=170,178)	2 (0 to 5)	1 (0.014 to 3)		
Serogroup A - hSBA ≥1:8 -Post-3rd dose(N=202,208)	76 (69 to 81)	1 (0 to 4)		
Serogroup C - hSBA ≥1:8 - Baseline(N=166,174)	7 (3 to 12)	7 (4 to 12)		
Serogroup C - hSBA ≥1:8 -Post-3rd dose(N=199,206)	94 (90 to 97)	1 (0 to 4)		
Serogroup W - hSBA ≥1:8 - Baseline(N=152,164)	13 (8 to 20)	15 (10 to 21)		
Serogroup W - hSBA ≥1:8 -Post-3rd dose(N=194,202)	98 (95 to 99)	3 (1 to 7)		
Serogroup Y - hSBA ≥1:8 - Baseline(N=144,150)	8 (4 to 13)	4 (1 to 9)		

Serogroup Y - hSBA ≥1:8 -Post-3rd dose(N=188,196)	94 (89 to 97)	3 (1 to 6)		
Serogroup A - 4-fold rise-Post-3rd dose(N=170,177)	78 (71 to 84)	2 (0 to 5)		
Serogroup C - 4-fold rise-Post-3rd dose(N=164,171)	94 (89 to 97)	1 (0 to 4)		
Serogroup W - 4-fold rise-Post-3rd dose(N=147,158)	93 (87 to 96)	2 (0 to 5)		
Serogroup Y -4-fold rise-Post-3rd dose(N=135,142)	93 (87 to 96)	2 (0 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 4. hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

End point title	4. hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

End point description:

Immunogenicity was measured as the hSBA GMTs directed against meningococcal serogroups A, C, W and Y before (baseline) and one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age.
Analysis was performed on the PP dataset of MenACWY-CRM infant vaccination series.

End point type	Secondary

End point timeframe:

Baseline and one month after three doses of infant series vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	209		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A - Baseline (N=170,178)	2.09 (2 to 2.18)	2.05 (1.98 to 2.12)		
Serogroup A - Post-3rd dose (N=202,208)	21 (17 to 26)	2.08 (1.99 to 2.17)		
Serogroup C - Baseline (N=166,174)	2.49 (2.25 to 2.76)	2.39 (2.18 to 2.61)		
Serogroup C - Post-3rd dose (N=199,206)	74 (62 to 87)	1.94 (1.64 to 2.3)		
Serogroup W - Baseline (N=152,164)	2.94 (2.52 to 3.43)	2.98 (2.58 to 3.45)		
Serogroup W - Post-3rd dose (N=194,202)	79 (67 to 92)	1.94 (1.68 to 2.24)		
Serogroup Y - Baseline (N=144,150)	2.52 (2.28 to 2.77)	2.26 (2.12 to 2.41)		
Serogroup Y - Post-3rd dose (N=188,196)	51 (43 to 61)	2.13 (2.02 to 2.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Percentage of Subjects With Immune Response to Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

End point title	5. Percentage of Subjects With Immune Response to Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

End point description:

The percentages of subjects with pre-specified cut-off limit of ≥ 0.1 IU/mL (Diphtheria and Tetanus); ≥ 0.15 µg/mL (Hib); ≥ 0.35 µg/mL (Pneumococcal antigens, PnC); and ≥ 10 mIU/mL (Hepatitis B) was evaluated using enzyme-linked immunosorbent assay (ELISA) at one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age.
The percentage of subjects with immune response against pertussis antigens (PT, FHA, Pertactin, FIM) (initially seronegative infants, ≥4 times the lower limit of quantification (LLQ); initially seropositive infants, at least 4 times prevaccination concentration) was measured by ELISA and percentage of subjects with titer ≥1:8 (Polio types 1,2,3) by neutralization test (NT) one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age. Analysis was performed on the PP concomitant infant population.

End point type	Secondary

End point timeframe:

One month after three doses of infant series vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	218		
Units: Percentage of subjects				
number (confidence interval 95%)				
Diphtheria (≥0.1 IU/mL)	99 (96 to 100)	99 (96 to 100)		
Tetanus (≥0.1 IU/mL)	97 (94 to 99)	97 (93 to 99)		
PT (N=185,191)	77 (71 to 83)	81 (75 to 86)		
FHA (N=185,191)	70 (63 to 76)	65 (58 to 72)		
Pertactin (N=185,191)	73 (66 to 79)	73 (66 to 79)		
FIM (N=185,191)	74 (67 to 80)	76 (69 to 82)		
Polio Type 1 - ≥1:8 (N=115,113)	99 (95 to 100)	98 (94 to 100)		
Polio Type 2 - ≥1:8 (N=185,179)	100 (98 to 100)	99 (97 to 100)		
Polio Type 3 - ≥1:8 (N=164,162)	99 (97 to 100)	100 (98 to 100)		
Hepatitis B - ≥10 mIU/mL (N=138,148)	96 (92 to 99)	97 (92 to 99)		
PRP-Hib - ≥0.15 µg/mL (N=187,194)	95 (90 to 97)	89 (84 to 93)		

PnC 4 - ≥0.35 µg/mL (N=183,178)	99 (96 to 100)	98 (94 to 99)		
PnC 6B - ≥0.35 µg/mL (N=183,178)	86 (80 to 91)	90 (84 to 94)		
PnC 9V - ≥0.35 µg/mL (N=183,178)	91 (86 to 95)	94 (90 to 97)		
PnC 14 - ≥0.35 µg/mL (N=183,178)	99 (96 to 100)	99 (96 to 100)		
PnC 18C - ≥0.35 µg/mL (N=183,178)	95 (90 to 97)	97 (94 to 99)		
PnC 19F - ≥0.35 µg/mL (N=183,178)	100 (98 to 100)	97 (93 to 99)		
PnC 23F - ≥0.35 µg/mL (N=183,178)	89 (83 to 93)	94 (89 to 97)		

Statistical analyses

Statistical analysis title	statistical analysis 1

Statistical analysis description:

To demonstrate the non-inferiority of immune response to diphtheria toxin, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	2.6

Notes:

[5] - Success criterion:
The immune response to diphtheria toxin, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

To demonstrate the non-inferiority of immune response to tetanus toxin, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	3.9

Notes:

[6] - Success criterion:
The immune response to tetanus toxin, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis toxin (PT), when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	4.3

Notes:

[7] - Success criterion:
The immune response to pertussis toxin (PT), when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis FHA antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	13.6

Notes:

[8] - Success criterion:
The immune response to pertussis FHA antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis pertactin antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	9.1

Notes:

[9] - Success criterion:
The immune response to pertussis pertactin antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis FIM antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	6.8

Notes:

[10] - Success criterion:
The immune response to pertussis FIM antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

To demonstrate the non-inferiority of immune response to hepatitis B antigen, when hepatitis B vaccine is given with MenACWY-CRM compared with when hepatitis B vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	4.5

Notes:

[11] - Success criterion:
The immune response to hepatitis B antigen, when hepatitis B vaccine is given concomitantly with MenACWY-CRM, was considered non-inferior to that of hepatitis B vaccine given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

To demonstrate the non-inferiority of immune response to Hib antigen, when Hib vaccine is given with MenACWY-CRM compared with when Hib vaccine is given alone.

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	11.2

Notes:

[12] - Success criterion:
The immune response to Hib vaccine, when given concomitantly with MenACWY-CRM, was considered non-inferior to that of Hib vaccine given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

To demonstrate the non-inferiority of immune response to polio antigen (Type 1), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	5.4

Notes:

[13] - Success criterion:
The immune response to polio antigen (Type 1), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the

difference in the percentage of subjects with antibody response was greater than or equal to -5%.

Statistical analysis title	Statistical analysis 10
Statistical analysis description:	
To demonstrate the non-inferiority of immune response to polio antigen (Type 2), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone	
Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3

Notes:

[14] - Success criterion:
The immune response to polio antigen (Type 2), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -5%.

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
To demonstrate the non-inferiority of immune response to polio antigen (Type 3), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone	
Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	1.7

Notes:

[15] - Success criterion:
The immune response to polio antigen (Type 3), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -5%.

Statistical analysis title	Statistical analysis 12
Statistical analysis description:	
To demonstrate the non-inferiority of immune response to pneumococcal PnC 4 antigen, when PCV is given with MenACWY-CRM, compared with when PCV is given alone	
Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines

Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	4.6

Notes:

[16] - Success criterion:
The immune response to pneumococcal PnC 4 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 6B antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	3.2

Notes:

[17] - Success criterion:
The immune response to pneumococcal PnC 6B antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 9V antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	2.3

Notes:

[18] - Success criterion:
The immune response to pneumococcal PnC 9V antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 14 antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	3

Notes:

[19] - Success criterion:
The immune response to pneumococcal PnC 14 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 18C antigen, when Pneumococcal Vaccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	1.6

Notes:

[20] - Success criterion:
The immune response to pneumococcal PnC 18C antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 19F antigen, when Pneumococcal Vaccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	7.1

Notes:

[21] - Success criterion:
The immune response to pneumococcal PnC 19F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 23F antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Method	Miettinen and Nurminen
Parameter estimate	vaccine group difference
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	0.5

Notes:

[22] - Success criterion:
The immune response to pneumococcal PnC 23F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

Secondary: 6. Geometric Mean Concentrations (GMCs) of Antibodies Against Routine

Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

End point title	6. Geometric Mean Concentrations (GMCs) of Antibodies Against Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

End point description:

The immune response was measured as the GMCs of antibodies directed against diphtheria, tetanus, pertussis (PT, FHA, Pertactin, FIM), hepatitis B, Hib, polio (type 1, 2 and 3) and pneumococcal (PnC 4, 6B, 9V, 14, 18C, 19F and 23F) antigens when routine vaccines are administered concomitantly with MenACWY-CRM compared with when routine vaccines are given alone, one month after three doses of infant series vaccination at 2, 4 and 6 months of age.
Analysis was performed on the PP concomitant infants population.

End point type	Secondary

End point timeframe:

One month after three doses of infant series vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	218		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Diphtheria	0.7 (0.63 to 0.78)	0.85 (0.76 to 0.94)		
Tetanus	0.8 (0.7 to 0.91)	0.67 (0.59 to 0.76)		
PT (N=185,191)	25 (21 to 30)	24 (21 to 29)		
FHA (N=185,191)	48 (43 to 54)	47 (42 to 52)		
Pertactin (N=185,191)	56 (47 to 65)	54 (46 to 62)		
FIM (N=185,191)	133 (113 to 157)	122 (105 to 143)		
Polio Type 1 (N=115,113)	149 (115 to 194)	117 (89 to 152)		
Polio Type 2 (N=185,179)	210 (178 to 246)	185 (156 to 218)		
Polio Type 3 (N=164,162)	457 (367 to 569)	402 (321 to 504)		
Hepatitis B (N=138,148)	394 (284 to 546)	402 (289 to 558)		
Hib (N=187,194)	3.75 (2.92 to 4.82)	2.76 (2.16 to 3.53)		
PnC 4 (N=183,178)	1.3 (1.16 to 1.46)	1.45 (1.29 to 1.63)		
PnC 6B (N=183,178)	1.42 (1.17 to 1.72)	1.79 (1.47 to 2.18)		
PnC 9V (N=183,178)	0.95 (0.84 to 1.08)	1.2 (1.05 to 1.36)		
PnC 14 (N=183,178)	6.31 (5.45 to 7.31)	6.61 (5.69 to 7.68)		
PnC 18C (N=183,178)	1.36 (1.2 to 1.55)	1.42 (1.24 to 1.62)		

PnC 19F (N=183,178)	1.84 (1.63 to 2.08)	2.04 (1.8 to 2.32)		
PnC 23F (N=183,178)	1.15 (0.99 to 1.35)	1.33 (1.13 to 1.56)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis toxin (PT), when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.28

Notes:

[23] - Success criterion:
The immune response measured as GMC of antibodies to pertussis toxin (PT), when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67

Statistical analysis title	Stastical analysis 2

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis FHA antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.19

Notes:

[24] - Success criterion:
The immune response measured as GMC of antibodies to pertussis FHA antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.

Statistical analysis title	Stastical analysis 3

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis pertactin antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	Routine Vaccines v MenACWY-CRM + Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.28

Notes:

[25] - Success criterion:
The immune response measured as GMC of antibodies to pertussis pertactin antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.

Statistical analysis title	Stastical analysis 4

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pertussis FIM antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.35

Notes:

[26] - Success criterion:
The immune response measured as GMC of antibodies to pertussis FIM antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.

Secondary: 7. GMCs of Antibodies Against Pneumococcal Antigens One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone

End point title	7. GMCs of Antibodies Against Pneumococcal Antigens One Month After Toddler Vaccination With PCV Administered With

	MenACWY-CRM Compared With PCV Given Alone

End point description:

Immunogenicity was measured as the GMCs of anti-pneumococcal antibodies against pneumococcal antigens PnC 4, 6B, 9V, 14, 18C, 19F and 23F, one month after toddler dose of PCV at 12 months of age administered concomitantly with MenACWY-CRM compared with PCV given alone.
Analysis was performed on the PP pneumococcal toddler population.

End point type	Secondary

End point timeframe:

One month after PCV toddler vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	170		
Units: µg/mL				
geometric mean (confidence interval 95%)				
PnC 4	1.57 (1.35 to 1.82)	1.6 (1.39 to 1.85)		
PnC 6B	5.92 (5.05 to 6.95)	7.8 (6.69 to 9.09)		
PnC 9V	1.67 (1.44 to 1.93)	1.91 (1.66 to 2.19)		
PnC 14	7.9 (6.73 to 9.28)	7.61 (6.52 to 8.88)		
PnC 18C	1.79 (1.55 to 2.08)	1.8 (1.57 to 2.08)		
PnC 19F	5.03 (4.36 to 5.82)	5.68 (4.95 to 6.53)		
PnC 23F	3.3 (2.8 to 3.89)	3.91 (3.34 to 4.57)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 4 antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	Routine Vaccines v MenACWY-CRM + Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.19

Notes:

[27] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 4 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 6B antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[28]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.93

Notes:

[28] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 6B antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 9V antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.06

Notes:

[29] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 9V antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 14 antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[30]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.28

Notes:

[30] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 14 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 18C antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone.

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[31]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.2

Notes:

[31] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 18C antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 19F antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines

Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[32]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.07

Notes:

[32] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 19F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 23F antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

Comparison groups	MenACWY-CRM + Routine Vaccines v Routine Vaccines
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
Method	ANOVA
Parameter estimate	vaccine group ratio of GMCs
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.04

Notes:

[33] - Success criterion:
The immune response as GMC of antibodies to pneumococcal PnC 23F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

Secondary: 8. Percentage of Subjects With Anti-pneumococcal Antigen Antibodies ≥0.35 µg/mL One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone

End point title	8. Percentage of Subjects With Anti-pneumococcal Antigen Antibodies ≥0.35 µg/mL One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone

End point description:

The immune response was measured as the percentage of subjects with anti-pneumococcal antigen antibodies ≥0.35 µg/mL against pneumococcal antigens PnC 4, 6B, 9V, 14, 18C, 19F and 23F, one month after toddler dose of PCV at 12 months of age when administered concomitantly with MenACWY-CRM compared with PCV given alone.
Analysis was performed on the PP pneumococcal toddler population.

End point type	Secondary

End point timeframe:

One month after PCV toddler vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	170		
Units: Percentage of subjects				
number (confidence interval 95%)				
PnC 4	93 (88 to 97)	96 (92 to 98)		
PnC 6B	99 (97 to 100)	98 (95 to 100)		
PnC 9V	97 (93 to 99)	96 (92 to 98)		
PnC 14	99 (96 to 100)	99 (97 to 100)		
PnC 18C	96 (92 to 99)	98 (94 to 99)		
PnC 19F (N=161,169)	99 (96 to 100)	100 (98 to 100)		
PnC 23F	99 (97 to 100)	98 (94 to 99)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Antibody Persistence by Percentage of Subjects With hSBA Titers ≥1:8 Against Serogroup A, C, W and Y at 12 Months of Age Prior to Toddler

End point title	9. Antibody Persistence by Percentage of Subjects With hSBA Titers ≥1:8 Against Serogroup A, C, W and Y at 12 Months of Age Prior to Toddler Vaccination

End point description:

The antibody persistence was measured as the percentage of subjects with hSBA titers ≥1:8 against meningococcal serogroup A, C, W and Y, at baseline and six months after three doses of infant series vaccination administered at 6 months (12 months of age), before administration of the toddler vaccination.
Analysis was performed on the PP toddler dataset for MenACWY-CRM.

End point type	Secondary

End point timeframe:

Baseline and six months after three doses of infant series vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	178		
Units: Percentage of subjects				
number (confidence interval 95%)				
Serogroup A - Baseline (N=139, 145)	1 (0 to 5)	0 (0 to 3)		

Serogroup A - 6 mo Post-3rd dose (N=168,175)	7 (4 to 12)	2 (0 to 5)		
Serogroup C - Baseline (N=126,136)	7 (3 to 13)	8 (4 to 14)		
Serogroup C - 6 mo Post-3rd dose (N=156,171)	37 (30 to 45)	2 (1 to 6)		
Serogroup W - Baseline (N=113,126)	15 (9 to 23)	15 (9 to 23)		
Serogroup W - 6 mo Post-3rd dose (N=153,165)	70 (62 to 77)	5 (2 to 9)		
Serogroup Y - Baseline (N=108,113)	6 (3 to 13)	5 (2 to 11)		
Serogroup Y - 6 mo Post-3rd dose (N=153,159)	53 (45 to 61)	3 (1 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Persistence of hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y, at 12 Months of Age, Prior to Toddler Vaccination

End point title	10. Persistence of hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y, at 12 Months of Age, Prior to Toddler Vaccination

End point description:

The antibody persistence was measured as the hSBA GMTs directed against meningococcal serogroup A, C, W and Y, at baseline and six months after third infant vaccination administered at 6 months (12 months of age), before administration of the toddler dose vaccination.
Analysis was performed on the PP toddler dataset for MenACWY-CRM.

End point type	Secondary

End point timeframe:

Baseline and six months after three doses of infant series vaccination

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	178		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A - Baseline (N=139, 145)	2.07 (1.98 to 2.16)	2.01 (1.99 to 2.03)		
Serogroup A - 6 mo Post-3rd dose (N=168,175)	2.52 (2.26 to 2.82)	2.12 (2 to 2.25)		
Serogroup C - Baseline (N=126,136)	2.49 (2.2 to 2.83)	2.44 (2.2 to 2.7)		
Serogroup C - 6 mo Post-3rd dose (N=156,171)	5.98 (4.81 to 7.43)	2.15 (2.02 to 2.3)		
Serogroup W - Baseline (N=113,126)	2.99 (2.49 to 3.6)	2.97 (2.52 to 3.51)		
Serogroup W - 6 mo Post-3rd dose (N=153,165)	15 (12 to 18)	2.23 (2.06 to 2.4)		
Serogroup Y - Baseline (N=108,113)	2.43 (2.19 to 2.71)	2.32 (2.13 to 2.52)		

Serogroup Y - 6 mo Post-3rd dose (N=153,159)	8.39 (6.9 to 10)	2.09 (2 to 2.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Percentage of Subjects With Four-fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point title	11. Percentage of Subjects With Four-fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Toddler Vaccination

End point description:

The immune response was measured as the percentage of subjects who achieved four-fold increase in hSBA titers against meningococcal serogroup A, C, W and Y one month after toddler vaccination administered at 12 months of age (compared to hSBA at Month 12, just before toddler dose). Analysis was performed on the PP toddler dataset for MenACWY-CRM.

End point type	Secondary

End point timeframe:

One month after toddler vaccination (month 13)

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	175		
Units: Percentage of subjects				
number (confidence interval 95%)				
Serogroup A (N=168,175)	89 (83 to 93)	1 (0.014 to 3)		
Serogroup C (N=156,171)	92 (87 to 96)	1 (0 to 4)		
Serogroup W (N=153,165)	95 (91 to 98)	2 (1 to 6)		
Serogroup Y (N=153,159)	96 (92 to 99)	1 (0.016 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12. Safety of MenACWY-CRM Vaccinations When Administered Concomitantly With Routine Vaccinations

End point title	12. Safety of MenACWY-CRM Vaccinations When Administered Concomitantly With Routine Vaccinations

End point description:

Safety of the study vaccines (MenACWY-CRM and other routine vaccines) was assessed in terms of the number of subjects who reported adverse events (AEs) and/or serious AEs per vaccine group at the following time points: entire study period, after infants vaccination (up to 7 months), between 2- and 4-months, between 4- and 6-months, between 6- and 12-months, between 7- and 12-months, 28 days

after 12-month vaccination, and between 29 days after 12-month vaccination and study termination. Solicited reactions were not collected during this study. The safety analyses also included any AEs observed by study personnel within 15 minutes following vaccination. All AEs and SAEs were judged by the investigator as probably related, possibly related, or not related to vaccine.
Analysis was done on Safety Set, i.e. all subjects in the exposed population who provide post-baseline safety data.

End point type	Secondary

End point timeframe:

From visit 1 (2 months of age) through visit 7 (18 months of age)

End point values	MenACWY-CRM + Routine Vaccines	Routine Vaccines		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	270		
Units: Percentage of subjects				
number (not applicable)				
Entire study - Any AEs	228	239		
Entire study - At least possibly related AEs	6	2		
Entire study - Serious AEs	21	20		
Up to 7 months - Any AEs	183	189		
Up to 7 months - At least possibly related AEs	6	1		
Up to 7 months - Serious AEs	7	8		
Between 2- and 4-months - Any AEs	99	105		
Between 2- & 4-mo - At least possibly related AEs	1	0		
Between 2- and 4-months - Serious AEs	5	5		
Between 4- and 6-months - Any AEs	118	114		
Between 4- & 6-mo - At least possibly related AEs	3	0		
Between 4- and 6-months - Serious AEs	2	2		
Between 6- and 12-months - Any AEs	187	197		
Between 6- & 12-mo - At least possibly related AEs	2	1		
Between 6- and 12-months - Serious AEs	10	2		
Between 7- and 12-months - Any AEs	175	181		
Between 7- & 12-mo - At least possibly related AEs	0	0		
Between 7- and 12-months - Serious AEs	9	2		
28 days post-toddler - Any AEs	80	78		
28 days post-toddler-At least possibly related AEs	0	0		
28 days post-toddler - Serious AEs	1	1		
Between 29 days and study termination - Any AEs	137	137		
B/w 29 days & study terminat-Possibly related AEs	0	0		
Between 29 days and study termination - SeriousAEs	7	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
from day 1 to 18 months	
Adverse event reporting additional description:	
The number of subjects reported here is from the safety set and not from the enrolled set.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Routine Vaccines
Reporting group description:	
Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	
Reporting group title	MenACWY-CRM + Routine Vaccines
Reporting group description:	
Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.	

Serious adverse events	Routine Vaccines	MenACWY-CRM + Routine Vaccines	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 270 (7.41%)	21 / 255 (8.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Moraxella Test Positive			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Laryngomalacia			

subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colectomy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive Disorder			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Convulsion			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Motility Disorder			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired Gastric Emptying			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal laceration			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory Distress			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 270 (0.74%)	4 / 255 (1.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			

subjects affected / exposed	2 / 270 (0.74%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 270 (0.74%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup Infectious			
subjects affected / exposed	3 / 270 (1.11%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Enteroviral			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus Infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Parainfluenzae Viral			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 270 (0.37%)	2 / 255 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Viral			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Bronchiolitis			
subjects affected / exposed	2 / 270 (0.74%)	3 / 255 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Abscess			
subjects affected / exposed	1 / 270 (0.37%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			

subjects affected / exposed	0 / 270 (0.00%)	1 / 255 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	2 / 270 (0.74%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure To Thrive			
subjects affected / exposed	1 / 270 (0.37%)	0 / 255 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Routine Vaccines	MenACWY-CRM + Routine Vaccines	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	227 / 270 (84.07%)	216 / 255 (84.71%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	45 / 270 (16.67%)	43 / 255 (16.86%)	
occurrences (all)	58	51	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 270 (8.89%)	18 / 255 (7.06%)	
occurrences (all)	24	18	
Diarrhoea			
subjects affected / exposed	26 / 270 (9.63%)	25 / 255 (9.80%)	
occurrences (all)	28	25	
Teething			

subjects affected / exposed	7 / 270 (2.59%)	16 / 255 (6.27%)	
occurrences (all)	7	18	
Vomiting			
subjects affected / exposed	31 / 270 (11.48%)	19 / 255 (7.45%)	
occurrences (all)	33	23	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	8 / 270 (2.96%)	15 / 255 (5.88%)	
occurrences (all)	9	15	
Cough			
subjects affected / exposed	27 / 270 (10.00%)	34 / 255 (13.33%)	
occurrences (all)	34	51	
Rhinitis allergic			
subjects affected / exposed	21 / 270 (7.78%)	17 / 255 (6.67%)	
occurrences (all)	31	33	
Wheezing			
subjects affected / exposed	8 / 270 (2.96%)	16 / 255 (6.27%)	
occurrences (all)	8	18	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	28 / 270 (10.37%)	29 / 255 (11.37%)	
occurrences (all)	30	29	
Dermatitis atopic			
subjects affected / exposed	17 / 270 (6.30%)	17 / 255 (6.67%)	
occurrences (all)	18	18	
Dermatitis diaper			
subjects affected / exposed	40 / 270 (14.81%)	33 / 255 (12.94%)	
occurrences (all)	47	46	
Rash			
subjects affected / exposed	15 / 270 (5.56%)	13 / 255 (5.10%)	
occurrences (all)	17	13	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	55 / 270 (20.37%)	60 / 255 (23.53%)	
occurrences (all)	74	63	
Bronchitis			

subjects affected / exposed	15 / 270 (5.56%)	15 / 255 (5.88%)	
occurrences (all)	16	17	
Bronchiolitis			
subjects affected / exposed	40 / 270 (14.81%)	37 / 255 (14.51%)	
occurrences (all)	50	44	
Candida nappy rash			
subjects affected / exposed	17 / 270 (6.30%)	6 / 255 (2.35%)	
occurrences (all)	19	6	
Candida infection			
subjects affected / exposed	24 / 270 (8.89%)	16 / 255 (6.27%)	
occurrences (all)	28	21	
Croup infectious			
subjects affected / exposed	21 / 270 (7.78%)	15 / 255 (5.88%)	
occurrences (all)	22	16	
Otitis media			
subjects affected / exposed	101 / 270 (37.41%)	100 / 255 (39.22%)	
occurrences (all)	226	249	
Gastroenteritis			
subjects affected / exposed	32 / 270 (11.85%)	38 / 255 (14.90%)	
occurrences (all)	37	44	
Otitis media acute			
subjects affected / exposed	31 / 270 (11.48%)	31 / 255 (12.16%)	
occurrences (all)	50	46	
Pharyngitis			
subjects affected / exposed	32 / 270 (11.85%)	24 / 255 (9.41%)	
occurrences (all)	43	27	
Rhinitis			
subjects affected / exposed	20 / 270 (7.41%)	19 / 255 (7.45%)	
occurrences (all)	20	19	
Sinusitis			
subjects affected / exposed	15 / 270 (5.56%)	10 / 255 (3.92%)	
occurrences (all)	15	21	
Upper respiratory tract infection			
subjects affected / exposed	154 / 270 (57.04%)	144 / 255 (56.47%)	
occurrences (all)	321	300	
Viral infection			

subjects affected / exposed occurrences (all)	51 / 270 (18.89%) 58	36 / 255 (14.12%) 49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2009	- The subjects in Group 2, the Control group will be administered one dose of MenACWY at Visit 7 with one month of follow up. This will extend the study period by 1 month, from 16 months to 17 months.
21 January 2010	- Need to clarify what vaccines can be administered and when they should be administered. - Need to clarify where injection should be given.
29 July 2011	- The protocol is being amended to reflect changes to the primary and secondary endpoints, and to describe the switch from Pre-Filled Syringe (PFS) to vial-vial presentation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported