Clinical trial results:
A Phase 3b, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Immunogenicity of 2 or 3 Doses of MenACWY Conjugate Vaccine in Healthy Infants and the Effects of a Booster Dose of MenACWY Administered in the Second Year of Life.

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

Summary

EudraCT number	2014-004577-16
Trial protocol	Outside EU/EEA
Global end of trial date	10 May 2012

Results information

Result version number	v2 (current)
This version publication date	01 June 2016
First version publication date	07 January 2015
Version creation reason	• Correction of full data set re-QC study because of EudraCT system glitch and updates to results are required including shifting of CI values.

Trial information

Trial identification

Sponsor protocol code	V59_36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01214837
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 Vaccines, RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines, 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	01 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity of a 3-dose vaccination schedule of MenACWY vaccine (2 infant doses at 2 and 4 months of age followed by a toddler dose at 12 months of age) compared to a 4-dose vaccination schedule (3 infant doses at 2, 4 and 6 months of age followed by a toddler dose at 12 months of age). The study also characterized immune responses following the first, second and third infant doses, and evaluated the effect of concomitant administration of MenACWY and PCV-13 on immune responses to PCV-13 antigens.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2010
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	Canada: 86
Country: Number of subjects enrolled	United States: 665
Worldwide total number of subjects	751
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)	751
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:

A total of 751 subjects were enrolled in this study, with 127 and 129 subjects following a 4-dose vaccination schedule of MenACWY (ACWY4a and ACWY4b groups, respectively), 249 subjects following a 3-dose vaccination schedule (ACWY3 group), and 246 subjects received routine vaccinations alone

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

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:

Laboratory staff was blinded to the study group allocation when processing serological samples.

Arms

Are arms mutually exclusive?	Yes
Arm title	MenACWY3

Arm description:

Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.

Arm type	Experimental
Investigational medicinal product name	Novartis meningococcal ACWY conjugate vaccine (MenACWY-CRM197, Menveo™) and Routine Vaccines, PCV 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL of dose was administered intra muscularly

Arm title	MenACWY4

Arm description:

Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.

Arm type	Experimental
Investigational medicinal product name	Novartis meningococcal ACWY conjugate vaccine (MenACWY-CRM197, Menveo™) and Routine Vaccines, PCV 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5mL of dose was administered intra muscularly

Arm title	Routine vaccines

Arm description:

Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.

Arm type	Routine Vaccines

Investigational medicinal product name	Routine Vaccines, PCV 13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Routine infant vaccines were to be administered to subjects according routine methods and schedules for the region.

Number of subjects in period 1	MenACWY3	MenACWY4	Routine vaccines
Started	249	256	246
Completed	195	192	184
Not completed	54	64	62
Adverse event, non-fatal	1	2	1
Death	-	-	1
Administrative Reason	2	6	4
Withdrawal by Subject	27	36	28
Inappropriate enrolment	-	1	2
Lost to follow-up	20	15	21
Unable to Classify	1	3	-
Protocol deviation	3	1	5

Baseline characteristics

Reporting groups	
Reporting group title	MenACWY3
Reporting group description:	
Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.	
Reporting group title	MenACWY4
Reporting group description:	
Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.	
Reporting group title	Routine vaccines
Reporting group description:	
Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.	

Reporting group values	MenACWY3	MenACWY4	Routine vaccines
Number of subjects	249	256	246
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	249	256	246
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: days			
arithmetic mean	66.4	66.7	66.7
standard deviation	± 7.1	± 7.4	± 7
Gender categorical Units: Subjects			
Female	126	123	106
Male	123	133	140

Reporting group values	Total		
Number of subjects	751		
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)	751		

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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	355		
Male	396		

End points

End points reporting groups

Reporting group title	MenACWY3
Reporting group description:	
Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.	
Reporting group title	MenACWY4
Reporting group description:	
Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.	
Reporting group title	Routine vaccines
Reporting group description:	
Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who had signed an informed consent, undergone screening procedure and were randomized.	
Subject analysis set title	Toddler PCV PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received doses of ACWY and PCV vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding through 13 month timepoint.	
Subject analysis set title	Toddler ACWY PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received doses of ACWY vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding through 13 month timepoint.	
Subject analysis set title	Solicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set with solicited adverse event data	
Subject analysis set title	Unsolicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set with unsolicited adverse event data.	
Subject analysis set title	Infant ACWY PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received doses of ACWY vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding, through the 7 month timepoint.	
Subject analysis set title	Infant PCV PPS
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects who received doses of ACWY and PCV vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding, through the 7 month timepoint.	

Primary: 1. Percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8, directed against N meningitidis serogroups A, C, W and Y.

End point title	1. Percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8, directed against N meningitidis serogroups A, C, W and Y.[1][2]

End point description:

The immune response was assessed in terms of percentage of subjects with hSBA ≥ 1:8 against N. meningitidis serogroups A, C, W and Y following 4 doses of Men ACWY vaccine given to infants at 2, 4, 6 and 12 months of age.
Analysis was done on the Toddler Per Protocol Population

End point type	Primary

End point timeframe:

13 months of age

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical null hypothesis associated with this immunogenicity objective.

[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	MenACWY4			
Subject group type	Reporting group			
Number of subjects analysed	152			
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A (N=141)	96 (91 to 98)			
Serogroup C	99 (95 to 100)			
Serogroup W (N=138)	99 (96 to 100)			
Serogroup Y (N=146)	99 (96 to 100)			

Statistical analyses

No statistical analyses for this end point

Primary: 2. Percentage of Subjects With hSBA ≥ 1:8 Against N Meningitidis Serogroups A, C, W and Y Following 4- Dose and 3-Dose Schedule of Men ACWY Vaccination.

End point title	2. Percentage of Subjects With hSBA ≥ 1:8 Against N Meningitidis Serogroups A, C, W and Y Following 4- Dose and 3-Dose Schedule of Men ACWY Vaccination.[3]

End point description:

The immune response was assessed in terms of percentage of subjects with hSBA ≥ 1:8 against N meningitidis serogroups A, C, W and Y following 4 doses of Men ACWY vaccine given to infants at 2, 4,6 and 12 months of age and 3 doses of Men ACWY given to infants at 2, 4 and 12 months of age.
Analysis was done on Toddler ACWY PPS.

End point type	Primary

End point timeframe:

13 months of age

Notes:

[3] - 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	MenACWY3	MenACWY4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	152		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A (N=146, 141)	88 (82 to 93)	96 (91 to 98)		
Serogroup C	95 (90 to 98)	99 (95 to 100)		
Serogroup W (N=153, 138)	99 (96 to 100)	99 (96 to 100)		
Serogroup Y (N-154, 146)	100 (98 to 100)	99 (96 to 100)		

Statistical analyses

Statistical analysis title	Percentage of Subjects With hSBA ≥ 1:8

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup A at 13 months of age.

Comparison groups	MenACWY4 v MenACWY3
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	Miettinen and Nurminen method
Parameter estimate	Group difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	-1

Notes:

[4] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers ≥ 1:8 against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

Statistical analysis title	Percentage of Subjects With hSBA ≥ 1:8

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup C at 13 months of age.

Comparison groups	MenACWY3 v MenACWY4
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	0

Notes:

[5] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers ≥ 1:8 against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

Statistical analysis title	Percentage of Subjects With hSBA ≥ 1:8

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup W at 13 months of age.

Comparison groups	MenACWY3 v MenACWY4
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	3

Notes:

[6] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers ≥ 1:8 against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

Statistical analysis title	Percentage of Subjects With hSBA ≥ 1:8

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup Y at 13 months of age.

Comparison groups	MenACWY3 v MenACWY4
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	4

Notes:

[7] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers ≥ 1:8 against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

Secondary: 3. Percentage of Subjects With hSBA ≥1:8 Against N. Meningitidis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.

End point title	3. Percentage of Subjects With hSBA ≥1:8 Against N. Meningitidis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.

End point description:

Antibody levels were assessed in terms of percentage of subjects with hSBA ≥ 1:8 against N. meningitidis serogroups A, C, W and Y at baseline (2 months of age) and at 3, 4, 5 and 7 months of age.

End point type	Secondary

End point timeframe:

Baseline (2 months of age), 3 months, 4 months , 5 months and 7 months of age

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	176	187	
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A (baseline; N=0,0,166)	0 (0 to 0)	0 (0 to 0)	4 (1 to 8)	
Serogroup A (3 months; N=0,82,0)	0 (0 to 0)	9 (4 to 17)	0 (0 to 0)	
Serogroup A (4 months; N=0,70,0)	0 (0 to 0)	4 (1 to 12)	0 (0 to 0)	
Serogroup A (5 months; N=157,0,0)	43 (35 to 51)	0 (0 to 0)	0 (0 to 0)	
Serogroup A (7 months; N=169,157,171)	23 (17 to 30)	84 (77 to 89)	1 (0.015 to 3)	
Serogroup C (baseline; N=0,0,167)	0 (0 to 0)	0 (0 to 0)	9 (5 to 14)	
Serogroup C (3 months; N=0,85,0)	0 (0 to 0)	28 (19 to 39)	0 (0 to 0)	
Serogroup C (4 months; N=0,70,0)	0 (0 to 0)	41 (30 to 54)	0 (0 to 0)	
Serogroup C (5 months; N=170,0,0)	86 (80 to 91)	0 (0 to 0)	0 (0 to 0)	
Serogroup C (7 months)	71 (64 to 78)	95 (91 to 98)	1 (0.014 to 3)	
Serogroup W (baseline; N=0,0,157)	0 (0 to 0)	0 (0 to 0)	20 (14 to 28)	
Serogroup W (3 months; N=0,84,0)	0 (0 to 0)	15 (9 to 25)	0 (0 to 0)	
Serogroup W (4 months; N=0,71,0)	0 (0 to 0)	35 (24 to 47)	0 (0 to 0)	
Serogroup W (5 months; N=162,0,0)	86 (80 to 91)	0 (0 to 0)	0 (0 to 0)	
Serogroup W (7 months; N=179,162,181)	74 (67 to 81)	99 (96 to 100)	1 (0.014 to 3)	
Serogroup Y (baseline; N=0,0,150)	0 (0 to 0)	0 (0 to 0)	7 (4 to 13)	
Serogroup Y (3 months; N=0,80,0)	0 (0 to 0)	8 (3 to 16)	0 (0 to 0)	
Serogroup Y (4 months; N=0,69,0)	0 (0 to 0)	7 (2 to 16)	0 (0 to 0)	
Serogroup Y (5 months; N=152,0,0)	67 (59 to 75)	0 (0 to 0)	0 (0 to 0)	
Serogroup Y (7 months; N=170,163,173)	48 (40 to 55)	94 (90 to 97)	0 (0 to 2)	

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Geometric Mean hSBA Titers Against N Meningitis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.

End point title	4. Geometric Mean hSBA Titers Against N Meningitis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.

End point description:

Antibody levels were assessed in terms of geometric mean titers (GMTs) against N. meningitidis serogroups A, C, W and Y at baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age. Analysis was done on the Infant ACWY PPS.

End point type	Secondary

End point timeframe:

Baseline (2 months of age), 3 months, 4 months , 5 months and 7 months of age

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	176	187	
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A (baseline; N=0,0,166)	0 (0 to 0)	0 (0 to 0)	2.18 (2.05 to 2.33)	
Serogroup A (3 months; N=0,82,0)	0 (0 to 0)	2.63 (2.2 to 3.15)	0 (0 to 0)	
Serogroup A (4 months; N=0,70,0)	0 (0 to 0)	2.18 (2 to 2.37)	0 (0 to 0)	
Serogroup A (5 months; N=157,0,0)	7.09 (5.62 to 8.94)	0 (0 to 0)	0 (0 to 0)	
Serogroup A (7 months; N=169,157,171)	3.68 (3.17 to 4.29)	28 (23 to 35)	2.02 (1.98 to 2.06)	
Serogroup C (baseline; N=0,0,167)	0 (0 to 0)	0 (0 to 0)	2.52 (2.28 to 2.78)	
Serogroup C (3 months; N=0,85,0)	0 (0 to 0)	4.79 (3.71 to 6.19)	0 (0 to 0)	
Serogroup C (4 months; N=0,70,0)	0 (0 to 0)	6.44 (4.83 to 8.59)	0 (0 to 0)	
Serogroup C (5 months; N=170,0,0)	50 (39 to 64)	0 (0 to 0)	0 (0 to 0)	
Serogroup C (7 months)	17 (14 to 22)	86 (70 to 104)	2.03 (1.97 to 2.08)	
Serogroup W (baseline; N=0,0,157)	0 (0 to 0)	0 (0 to 0)	3.32 (2.82 to 3.9)	
Serogroup W (3 months; N=0,84,0)	0 (0 to 0)	3 (2.48 to 3.61)	0 (0 to 0)	
Serogroup W (4 months; N=0,71,0)	0 (0 to 0)	4.38 (3.42 to 5.61)	0 (0 to 0)	
Serogroup W (5 months; N=162,0,0)	55 (42 to 71)	0 (0 to 0)	0 (0 to 0)	
Serogroup W (7 months; N=179,162,181)	17 (14 to 21)	90 (77 to 104)	2.04 (1.96 to 2.11)	
Serogroup Y (baseline; N=0,0,150)	0 (0 to 0)	0 (0 to 0)	2.47 (2.25 to 2.7)	
Serogroup Y (3 months; N=0,80,0)	0 (0 to 0)	2.5 (2.14 to 2.93)	0 (0 to 0)	
Serogroup Y (4 months; N=0,69,0)	0 (0 to 0)	2.46 (2.16 to 2.79)	0 (0 to 0)	

Serogroup Y (5 months; N=152,0,0)	20 (15 to 26)	0 (0 to 0)	0 (0 to 0)	
Serogroup Y (7 months; N=170,163,173)	7.56 (6.29 to 9.08)	52 (43 to 64)	2 (2 to 2)	

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Percentage of Subjects With hSBA ≥1:8 Following 2 and 3 Infant Doses of MenACWY.

End point title	5. Percentage of Subjects With hSBA ≥1:8 Following 2 and 3 Infant Doses of MenACWY.[8]

End point description:

Percentage of subjects with hSBA ≥1:8 against N meningitis serogroups A, C, W and Y was assessed following 2 and 3 infant doses of MenACWY as measured prior to the toddler dose at 12 months of age.

End point type	Secondary

End point timeframe:

Percentage of Subjects With hSBA ≥1:8 Following 2 and 3 Infant Doses of MenACWY.

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	MenACWY3	MenACWY4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	147		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A (N=141,138)	6 (2 to 11)	22 (15 to 30)		
Serogroup C	19 (13 to 27)	48 (39 to 56)		
Serogroup W (N=149,142)	33 (25 to 41)	66 (58 to 74)		
Serogroup Y (N=145,139)	25 (18 to 33)	55 (47 to 64)		

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Geometric Mean hSBA Titers Following 2 and 3 Infant Doses of MenACWY

End point title	6. Geometric Mean hSBA Titers Following 2 and 3 Infant Doses of MenACWY[9]

End point description:

The immune response was assessed in terms of GMTs against N. meningitidis serogroups A, C, W and Y following 2 and 3 infant doses of MenACWY as measured prior to the toddler dose at 12 months of age.

End point type	Secondary

End point timeframe:

12 months of age.

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	MenACWY3	MenACWY4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	147		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A (N=141,138)	2.28 (2.09 to 2.49)	3.65 (3.08 to 4.33)		
Serogroup C	3.54 (2.99 to 4.17)	8.55 (6.75 to 11)		
Serogroup W (N=149,142)	5.41 (4.39 to 6.67)	13 (11 to 16)		
Serogroup Y (N=145,139)	3.82 (3.24 to 4.49)	9.65 (7.79 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7. GMTs at 13 Months of Age After Completion of 3- and 4-Dose Series of MenACWY.

End point title	7. GMTs at 13 Months of Age After Completion of 3- and 4-Dose Series of MenACWY.[10]

End point description:

Immune response was assessed in terms of GMTs against N meningitis serogroups A, C, W and Y at 1 month after completion of a 3- and 4- dose series of MenACWY.
Analysis was done on the Toddler ACWY PPS.

End point type	Secondary

End point timeframe:

13 months of age

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	MenACWY3	MenACWY4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	152		
Units: Titers				
geometric mean (confidence interval 95%)				
Serogroup A (N=146,141)	59 (45 to 77)	94 (76 to 117)		
Serogroup C	124 (99 to 156)	160 (130 to 198)		
Serogroup W (N=153,138)	248 (202 to 303)	244 (195 to 305)		
Serogroup Y (N=154,146)	212 (175 to 258)	254 (203 to 318)		

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Percentage of Subjects With 4-fold Increase in hSBA Titers Against N Meningitis Serogroups A, C, W and Y Between 12 and 13 Months of Age.

End point title	8. Percentage of Subjects With 4-fold Increase in hSBA Titers Against N Meningitis Serogroups A, C, W and Y Between 12 and 13 Months of Age.[11]

End point description:

The immune response was assessed in terms of percentage of subjects with 4-fold increase in hSBA titers between post and pre toddler dose against N meningitis serogroups A, C, W and Y, 1 month after completing a 3- or 4-dose series of MenACWY.
Analysis was done on the Toddler PPS.

End point type	Secondary

End point timeframe:

13 months of age

Notes:

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

End point values	MenACWY3	MenACWY4		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	147		
Units: Percentages of Subjects				
number (confidence interval 95%)				
Serogroup A (N=127,129)	88 (81 to 93)	95 (90 to 98)		
Serogroup C	93 (88 to 97)	91 (85 to 95)		
Serogroup W (N=140,131)	98 (94 to 100)	90 (84 to 95)		
Serogroup Y (N=139,136)	100 (97 to 100)	96 (91 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Effect of Concomitant Administration of 3 or 4 Doses of MenACWY on Immune Response to PCV-13 Antigens at 13 Months of Age.

End point title	9. Effect of Concomitant Administration of 3 or 4 Doses of MenACWY on Immune Response to PCV-13 Antigens at 13 Months of Age.

End point description:

Geometric mean concentrations (GMCs) of antibodies against PCV-13 vaccine antigens at 13 months of age following concomitant administration of a 3- or 4-dose series of MenACWY with PCV-13.

Analysis was done on the Toddler PCV PPS.

End point type	Secondary
End point timeframe: 13 months of age.	

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	117	124	
Units: µg/mL				
geometric mean (confidence interval 95%)				
1 (N=145,116,123)	2 (1.7 to 2.36)	2.16 (1.83 to 2.56)	2.14 (1.8 to 2.54)	
3 (N=139,113,118)	0.88 (0.74 to 1.05)	0.97 (0.81 to 1.15)	0.77 (0.64 to 0.93)	
4 (N=146,117,123)	1.19 (0.99 to 1.42)	1.45 (1.21 to 1.75)	1.53 (1.27 to 1.86)	
5 (N=140,114,117)	1.29 (1.11 to 1.49)	1.35 (1.16 to 1.57)	1.26 (1.08 to 1.48)	
6A (N=146,117,124)	6.89 (5.78 to 8.21)	9.01 (7.52 to 11)	8.16 (6.77 to 9.82)	
6B (N=147,117,124)	4.29 (3.6 to 5.11)	5.23 (4.36 to 6.27)	5.04 (4.18 to 6.08)	
7F (N=147,116,123)	3.96 (3.42 to 4.58)	5.14 (4.41 to 5.98)	4.95 (4.23 to 5.78)	
9V (N=146,117,123)	1.37 (1.17 to 1.61)	1.85 (1.56 to 2.18)	1.73 (1.46 to 2.05)	
14 (N=147,117,124)	7.76 (6.51 to 9.26)	7.86 (6.55 to 9.43)	7.54 (6.25 to 9.09)	
18C (N=146,116,123)	1.52 (1.28 to 1.8)	2.34 (1.96 to 2.79)	2.13 (1.78 to 2.55)	
19A (N=144,114,124)	5.51 (4.61 to 6.6)	5.23 (4.34 to 6.3)	5.39 (4.45 to 6.51)	
19F (N=147,117,124)	5.79 (4.9 to 6.85)	6.19 (5.21 to 7.35)	5.8 (4.86 to 6.92)	
23F (N=147,117,124)	4.21 (3.49 to 5.09)	4.84 (3.98 to 5.89)	5.44 (4.45 to 6.65)	

Statistical analyses

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 1)
Statistical analysis description: To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 1.	
Comparison groups	MenACWY3 v Routine vaccines

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.13

Notes:

[12] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (Serotype 1)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 1.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.25

Notes:

[13] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 3)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 3.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.4

Notes:

[14] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (Serotype 3)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 3.

Comparison groups	Routine vaccines v MenACWY4
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.55

Notes:

[15] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 4)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 4.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.96

Notes:

[16] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 4)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 4.

Comparison groups	Routine vaccines v MenACWY4

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.18

Notes:

[17] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 5)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 5.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[18]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.21

Notes:

[18] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (Serotype 5)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 5.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[19]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.29

Notes:

[19] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 6A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6A.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[20]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.04

Notes:

[20] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 6A)
Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.37

Notes:

[21] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 6B)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6B.

Comparison groups	MenACWY3 v Routine vaccines

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[22]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.05

Notes:

[22] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 6B)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6B.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.3

Notes:

[23] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 7F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 7F.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.95

Notes:

[24] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 7F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 7F.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.25

Notes:

[25] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 9V)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 9V.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[26]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.96

Notes:

[26] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 9V)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 9V.

Comparison groups	MenACWY4 v Routine vaccines

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.31

Notes:

[27] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 14)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 14.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[28]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.27

Notes:

[28] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 14)

Statistical analysis description:

demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 14.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[29]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.3

Notes:

[29] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 18C)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 18C.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[30]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.87

Notes:

[30] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 18C)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 18C.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[31]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.36

Notes:

[31] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 19A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19A.

Comparison groups	MenACWY3 v Routine vaccines

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[32]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.27

Notes:

[32] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 19A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19A.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.21

Notes:

[33] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 19F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19F.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[34]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.22

Notes:

[34] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 19F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19F.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[35]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.32

Notes:

[35] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 23F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 23F.

Comparison groups	Routine vaccines v MenACWY3
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	non-inferiority[36]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.97

Notes:

[36] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY3 to routine vaccines) is greater than 0.5.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 23F)
Comparison groups	MenACWY4 v Routine vaccines

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[37]
Method	ANOVA
Parameter estimate	GMC ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.13

Notes:

[37] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

Secondary: 10. Effect of Concomitant Administration of 2 or 3 Doses of MenACWY on Immune Response to PCV-13 Antigens at 7 Months of Age.

End point title	10. Effect of Concomitant Administration of 2 or 3 Doses of MenACWY on Immune Response to PCV-13 Antigens at 7 Months of Age.

End point description:

Percentage of subjects with IgG concentration ≥ 0.35 µg/mL against pneumococcal conjugate vaccine (PCV-13) antigens at 7 Months of age following concomitant administration of 2 or 3 doses of MenACWY with PCV-13.
Analysis was done on Infant PCV PPS

End point type	Secondary

End point timeframe:

7 months of age.

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	137	158	
Units: Percentages of Subjects				
number (confidence interval 95%)				
1 (N=159,136,156)	93.7 (88.7 to 96.9)	100 (97.3 to 100)	94.2 (89.3 to 97.3)	
3 (N=150,129,147)	79.3 (72 to 85.5)	87.6 (80.6 to 92.7)	82.3 (75.2 to 88.1)	
4 (N=160,137,157)	94.4 (89.6 to 97.4)	97.1 (92.7 to 99.2)	96.8 (92.7 to 99)	
5 (N=156,133,154)	84 (77.3 to 89.4)	93.2 (87.5 to 96.9)	88.3 (82.2 to 92.9)	
6A (N=159,136,156)	98.1 (94.6 to 99.6)	99.3 (96 to 100)	98.1 (94.5 to 99.6)	
6B (N=160,137,157)	84.4 (77.8 to 89.6)	94.9 (89.8 to 97.9)	84.7 (78.1 to 90)	
7F (N=158,136,156)	100 (97.7 to 100)	100 (97.3 to 100)	99.4 (96.5 to 100)	
9V (N=159,136,157)	89.3 (83.4 to 93.6)	96.3 (91.6 to 98.8)	92.4 (87 to 96)	
14 (N=158,136,158)	99.4 (96.5 to 100)	100 (97.3 to 100)	97.5 (93.6 to 99.3)	

18C (N=158,136,157)	97.5 (93.6 to 99.3)	97.8 (93.7 to 99.5)	100 (97.7 to 100)	
19A (N=158,135,156)	95.6 (91.1 to 98.2)	92.6 (86.8 to 96.4)	98.1 (94.5 to 99.6)	
19F (N=159,136,158)	100 (97.7 to 100)	100 (97.3 to 100)	99.4 (96.5 to 100)	
23F (N=158,136,158)	93 (87.9 to 96.5)	95.6 (90.6 to 98.4)	91.1 (85.6 to 98.4)	

Statistical analyses

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 1)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 1.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[38]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	5

Notes:

[38] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine Vaccines (Serotype 1)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 1.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[39]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	10.5

Notes:

[39] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine Vaccines (Serotype 3)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 3.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[40]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	6

Notes:

[40] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 3)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 3.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[41]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	13.7

Notes:

[41] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 4)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 4.

Comparison groups	MenACWY3 v Routine vaccines

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[42]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	2.3

Notes:

[42] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 4)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 4.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[43]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	4.7

Notes:

[43] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine Vaccines (serotype 5)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 5.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[44]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	3.4

Notes:

[44] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine Vaccines (serotype 5)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 5.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[45]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	11.8

Notes:

[45] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serogroup 6A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6A.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[46]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	3.8

Notes:

[46] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serogroup 6A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6A.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[47]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	4.8

Notes:

[47] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serogroup 6B)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6B.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[48]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	7.7

Notes:

[48] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serogroup 6B)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6B.

Comparison groups	MenACWY4 v Routine vaccines

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[49]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	17.2

Notes:

[49] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 7F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 7F.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[50]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	3.5

Notes:

[50] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 7F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 7F.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[51]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	3.5

Notes:

[51] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 9V)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 9V.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[52]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	3.4

Notes:

[52] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 9V)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 9V.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[53]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	9.7

Notes:

[53] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 14)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 14.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[54]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	5.7

Notes:

[54] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 14)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 14.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[55]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	6.3

Notes:

[55] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 18C)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 18C.

Comparison groups	MenACWY3 v Routine vaccines

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[56]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-0.2

Notes:

[56] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 18C)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 18C.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[57]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	-0.2

Notes:

[57] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 19A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19A

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[58]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	1.6

Notes:

[58] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 19A)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19A.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[59]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	-0.9

Notes:

[59] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 19F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19F

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[60]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	3.4

Notes:

[60] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

	MenACWY4 vs Routine vaccines (serotype 19F)

Statistical analysis title	

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19F.

Comparison groups	MenACWY4 v Routine vaccines
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[61]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	3.4

Notes:

[61] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY3 vs Routine vaccines (serotype 23F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 23F.

Comparison groups	MenACWY3 v Routine vaccines
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority[62]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	8.2

Notes:

[62] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Statistical analysis title	MenACWY4 vs Routine vaccines (serotype 23F)

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 23F

Comparison groups	MenACWY4 v Routine vaccines

Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	non-inferiority[63]
Method	Miettinen and Nurminen method
Parameter estimate	Risk difference (RD)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	10.5

Notes:

[63] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration ≥ 0.35 µg/mL against each pneumococcal anti-capsular polysaccharide is greater than -10%.

Secondary: 11. Percentage Of Subjects Reporting at Least One Severe Systemic Solicited Adverse Event

End point title	11. Percentage Of Subjects Reporting at Least One Severe Systemic Solicited Adverse Event

End point description:

Safety was assessed as the percentage of subjects who reported severe solicited systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

End point type	Secondary

End point timeframe:

Day 1 through Day 7

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238	240	230	
Units: Percentage of Subjects				
number (not applicable)				
At least one severe systemic solicited AE	18	21	18	

Statistical analyses

No statistical analyses for this end point

Secondary: 12. Number Of Subjects Reporting Solicited Local or Systemic Adverse Events after any vaccination.

End point title	12. Number Of Subjects Reporting Solicited Local or Systemic Adverse Events after any vaccination.

End point description:

Safety was assessed as the number of subjects who reported solicited local or systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

End point type	Secondary

End point timeframe:

Day 1 (6 hour) to day 7

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	238	239	229	
Units: Subjects				
number (not applicable)				
Injection site erythema	72	64	79	
Injection site induration	60	40	74	
Tenderness	117	127	126	
Change in eating habits (N=238,238,229)	104	104	93	
Sleepiness	153	147	149	
Persistent crying	140	137	112	
Irritability	173	171	152	
Vomiting	68	52	54	
Diarrhea	89	69	68	
Fever (≥38.0°C)	55	52	41	
Rash	23	19	18	
Use of analgesic/antipyretic	162	173	153	

Statistical analyses

No statistical analyses for this end point

Secondary: 13. Number of Subjects Reporting Unsolicited Adverse Events After Any Vaccination

End point title	13. Number of Subjects Reporting Unsolicited Adverse Events After Any Vaccination

End point description:

Safety was assessed as the number of subjects who reported unsolicited local or systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

End point type	Secondary

End point timeframe:

2 months to 13 months of age.

End point values	MenACWY3	MenACWY4	Routine vaccines	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	242	252	239	
Units: Subjects				
number (not applicable)				
Any AE	219	220	209	
At least possibly related AEs	24	32	10	
SAEs	11	19	11	

Deaths	0	0	1	
Medically attended AEs	210	211	198	
AEs resulting in premature withdrawal	1	2	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 months to 13 months of age

Adverse event reporting additional description:

Solicited local and systemic and unsolicited AEs were assessed for 7 days postvaccination. Medically attended AEs and SAEs were collected throughout the study period

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	MenACWY3

Reporting group description:

Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.

Reporting group title	MenACWY4

Reporting group description:

Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.

Reporting group title	Routine vaccines

Reporting group description:

Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.

Serious adverse events	MenACWY3	MenACWY4	Routine vaccines
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 242 (4.55%)	19 / 252 (7.54%)	11 / 239 (4.60%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Congenital, familial and genetic disorders			
Congenital megacolon			

subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Krabbe's disease			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Laryngomalacia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 242 (0.00%)	2 / 252 (0.79%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nystagmus			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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
Pneumomediastinum			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Pneumonitis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory acidosis			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Breath holding			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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
Abscess			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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	2 / 242 (0.83%)	2 / 252 (0.79%)	4 / 239 (1.67%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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
Croup infectious			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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
Influenza			

subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Otitis media acute			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
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 / 242 (0.41%)	1 / 252 (0.40%)	0 / 239 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 242 (0.00%)	1 / 252 (0.40%)	0 / 239 (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 synctial virus bronchiolitis			
subjects affected / exposed	2 / 242 (0.83%)	5 / 252 (1.98%)	2 / 239 (0.84%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal abscess			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Failure to thrive			

subjects affected / exposed	1 / 242 (0.41%)	0 / 252 (0.00%)	0 / 239 (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
Hyperkalaemia			
subjects affected / exposed	0 / 242 (0.00%)	0 / 252 (0.00%)	1 / 239 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	MenACWY3	MenACWY4	Routine vaccines
Total subjects affected by non-serious adverse events			
subjects affected / exposed	238 / 242 (98.35%)	233 / 252 (92.46%)	228 / 239 (95.40%)
Nervous system disorders			
Somnolence			
alternative assessment type: Systematic			
subjects affected / exposed	162 / 242 (66.94%)	154 / 252 (61.11%)	158 / 239 (66.11%)
occurrences (all)	400	363	377
General disorders and administration site conditions			
Crying			
subjects affected / exposed	140 / 242 (57.85%)	138 / 252 (54.76%)	112 / 239 (46.86%)
occurrences (all)	227	259	220
Injection site induration			
subjects affected / exposed	65 / 242 (26.86%)	45 / 252 (17.86%)	79 / 239 (33.05%)
occurrences (all)	93	72	138
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	87 / 242 (35.95%)	80 / 252 (31.75%)	89 / 239 (37.24%)
occurrences (all)	139	164	160
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	137 / 242 (56.61%)	140 / 252 (55.56%)	138 / 239 (57.74%)
occurrences (all)	286	282	266
Pyrexia			
alternative assessment type: Systematic			

subjects affected / exposed	88 / 242 (36.36%)	88 / 252 (34.92%)	69 / 239 (28.87%)
occurrences (all)	138	141	105
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	13 / 242 (5.37%)	10 / 252 (3.97%)	9 / 239 (3.77%)
occurrences (all)	16	12	12
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 242 (4.13%)	21 / 252 (8.33%)	19 / 239 (7.95%)
occurrences (all)	11	23	21
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	103 / 242 (42.56%)	78 / 252 (30.95%)	80 / 239 (33.47%)
occurrences (all)	180	143	138
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 242 (4.55%)	14 / 252 (5.56%)	27 / 239 (11.30%)
occurrences (all)	11	14	30
Teething			
subjects affected / exposed	15 / 242 (6.20%)	13 / 252 (5.16%)	19 / 239 (7.95%)
occurrences (all)	16	14	24
Vomiting			
subjects affected / exposed	76 / 242 (31.40%)	68 / 252 (26.98%)	67 / 239 (28.03%)
occurrences (all)	127	99	110
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 242 (13.22%)	32 / 252 (12.70%)	37 / 239 (15.48%)
occurrences (all)	33	34	44
Wheezing			
subjects affected / exposed	12 / 242 (4.96%)	9 / 252 (3.57%)	16 / 239 (6.69%)
occurrences (all)	12	9	20
Nasal congestion			
subjects affected / exposed	16 / 242 (6.61%)	18 / 252 (7.14%)	14 / 239 (5.86%)
occurrences (all)	18	22	18
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	10 / 242 (4.13%)	11 / 252 (4.37%)	14 / 239 (5.86%)
occurrences (all)	13	12	16
Eczema			
subjects affected / exposed	16 / 242 (6.61%)	19 / 252 (7.54%)	20 / 239 (8.37%)
occurrences (all)	18	19	22
Dermatitis diaper			
subjects affected / exposed	38 / 242 (15.70%)	31 / 252 (12.30%)	22 / 239 (9.21%)
occurrences (all)	41	38	33
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	29 / 242 (11.98%)	31 / 252 (12.30%)	36 / 239 (15.06%)
occurrences (all)	34	37	47
Psychiatric disorders			
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	181 / 242 (74.79%)	179 / 252 (71.03%)	157 / 239 (65.69%)
occurrences (all)	479	459	399
Eating disorder			
alternative assessment type: Systematic			
subjects affected / exposed	104 / 242 (42.98%)	104 / 252 (41.27%)	93 / 239 (38.91%)
occurrences (all)	195	189	152
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	42 / 242 (17.36%)	25 / 252 (9.92%)	40 / 239 (16.74%)
occurrences (all)	51	31	44
Bronchiolitis			
subjects affected / exposed	34 / 242 (14.05%)	36 / 252 (14.29%)	30 / 239 (12.55%)
occurrences (all)	41	46	36
Candida nappy rash			
subjects affected / exposed	13 / 242 (5.37%)	6 / 252 (2.38%)	7 / 239 (2.93%)
occurrences (all)	14	7	7
Bronchitis			
subjects affected / exposed	8 / 242 (3.31%)	19 / 252 (7.54%)	17 / 239 (7.11%)
occurrences (all)	9	24	18
Candidiasis			

subjects affected / exposed	14 / 242 (5.79%)	20 / 252 (7.94%)	21 / 239 (8.79%)
occurrences (all)	15	23	22
Croup Infectious			
subjects affected / exposed	13 / 242 (5.37%)	16 / 252 (6.35%)	16 / 239 (6.69%)
occurrences (all)	13	17	19
Gastroenteritis			
subjects affected / exposed	22 / 242 (9.09%)	18 / 252 (7.14%)	27 / 239 (11.30%)
occurrences (all)	26	21	30
Otitis media			
subjects affected / exposed	94 / 242 (38.84%)	77 / 252 (30.56%)	89 / 239 (37.24%)
occurrences (all)	193	153	183
Rhinitis			
subjects affected / exposed	20 / 242 (8.26%)	17 / 252 (6.75%)	15 / 239 (6.28%)
occurrences (all)	25	26	20
Otitis media acute			
subjects affected / exposed	23 / 242 (9.50%)	19 / 252 (7.54%)	16 / 239 (6.69%)
occurrences (all)	31	24	29
Sinusitis			
subjects affected / exposed	9 / 242 (3.72%)	17 / 252 (6.75%)	7 / 239 (2.93%)
occurrences (all)	10	21	8
Viral infection			
subjects affected / exposed	38 / 242 (15.70%)	32 / 252 (12.70%)	30 / 239 (12.55%)
occurrences (all)	42	38	37
Upper respiratory tract infection			
subjects affected / exposed	105 / 242 (43.39%)	107 / 252 (42.46%)	106 / 239 (44.35%)
occurrences (all)	192	186	194
Viral rash			
subjects affected / exposed	10 / 242 (4.13%)	10 / 252 (3.97%)	13 / 239 (5.44%)
occurrences (all)	10	12	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2011	A secondary objective was added to compare persistence of 2 vs 3-dose infant series at 12 months of age; 4-fold rise in hSBA added as an endpoint for evaluating immune response at 13 months of age (ie, following the toddler dose).
10 May 2012	Added primary objective added, to demonstrate a sufficient immune response of 4 doses of MenACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) ≥1:8, directed against N meningitidis serogroups A, C, W and Y. Added description of tiered approach of assessing noninterference of PCV-13 concomitantly administered with MenACWY, using a hierarchical sequential testing procedure that groups the serotypes into 2 families.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 July 2011	FDA/CBER imposed a formal partial clinical hold due to insufficient information to assess the risks to subjects of translucent particles detected in the prefilled syringes (PFS) used in ongoing studies. All study sites in Canada and the USA were notified via letter to immediately stop using the PFS/vial presentation, to quarantine all doses, and to immediately switch to the vial/vial vaccine presentation.	26 July 2011

Notes:

Limitations and caveats

None reported