



Clinical trial results:

A Phase 3b, Randomized, Observer-Blind, Placebo-Controlled Multicenter Study Comparing Immunogenicity, Safety and 1 Year Persistence of Antibodies after either One or Two Doses of Novartis Meningococcal ACWY Conjugate Vaccine, administered to Healthy Children 2 to 10 years of age.

Summary

EudraCT number	2011-004421-27
Trial protocol	HU
Global end of trial date	30 May 2014

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	25 April 2015

Trial information

Trial identification

Sponsor protocol code	V59_57
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01682876
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	13 November 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate noninferiority of 2 doses (given 2 months apart) versus 1 dose of meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM-197 conjugate (MenACWY-CRM) vaccine, by age group (2 to 5 years of age; 6 to 10 years of age), as measured by the percentage of subjects with a serum bactericidal assay using human complement (hSBA) seroresponse directed against N meningitidis serogroups A, C, W and Y, at 1 month after last vaccination.

2. To demonstrate superiority of 2 doses (given 2 months apart) versus 1 dose of MenACWY-CRM vaccine, by age group (2 to 5 years of age; 6 to 10 years of age), as measured by the percentage of subjects with hSBA seroresponse directed against N meningitidis serogroups A, C, W and Y, at 1 month after last vaccination.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, United States (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	07 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 715
Worldwide total number of subjects	715
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)	0
Children (2-11 years)	715
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 22 locations.

Pre-assignment

Screening details:

All enrolled subjects were included in the trial.

Period 1

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

Blinding implementation details:

During the study, unblinded qualified health care personnel administered the study vaccine or placebo to the subjects, and were instructed not to reveal the identity of the study vaccine/placebo to the subject/subject's parents/legal guardians or to the investigative site personnel monitoring or conducting the study, except in emergency situations. Information on study vaccine/placebo allocations was not available to the investigator or monitoring personnel until completion of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	2 Through 5 Years (2 Vac)

Arm description:

Subjects 2-5 years of age received two MenACWY-CRM vaccinations.

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

Dosage and administration details:

2 doses of 0.5 mL

Arm title	2 Through 5 Years (1 Vac)
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Arm description:

Subjects 2-5 years of age received one MenACWY-CRM vaccination.

Arm type	Placebo 1st vac, active comparator 2nd vac
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 0.5 mL

Arm title	6 Through 10 Years (2 Vac)
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Arm description:

Subjects 6-10 years of age received two MenACWY-CRM vaccinations.

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

Dosage and administration details:

2 doses of 0.5 mL

Arm title	6 Through 10 Years (1 Vac)
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Arm description:

Subjects 6-10 years of age received one MenACWY-CRM vaccination.

Arm type	Placebo 1st vac, active comparator 2nd vac
Investigational medicinal product name	Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 0.5 mL

Number of subjects in period 1	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)
Started	176	183	180
Completed	155	163	169
Not completed	21	20	11
Consent withdrawn by subject	4	-	-
Adverse Event	-	-	-
Other	1	-	1
Administrative Reason	4	4	-
Lost to follow-up	11	15	9
Protocol deviation	1	1	1

Number of subjects in period 1	6 Through 10 Years (1 Vac)
Started	176
Completed	157
Not completed	19
Consent withdrawn by subject	2
Adverse Event	1
Other	1
Administrative Reason	3
Lost to follow-up	11
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	2 Through 5 Years (2 Vac)
Reporting group description:	
Subjects 2-5 years of age received two MenACWY-CRM vaccinations.	
Reporting group title	2 Through 5 Years (1 Vac)
Reporting group description:	
Subjects 2-5 years of age received one MenACWY-CRM vaccination.	
Reporting group title	6 Through 10 Years (2 Vac)
Reporting group description:	
Subjects 6-10 years of age received two MenACWY-CRM vaccinations.	
Reporting group title	6 Through 10 Years (1 Vac)
Reporting group description:	
Subjects 6-10 years of age received one MenACWY-CRM vaccination.	

Reporting group values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)
Number of subjects	176	183	180
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	3.5	3.6	7.8
standard deviation	± 1.1	± 1.2	± 1.4
Gender categorical Units: Subjects			
Female	84	88	97
Male	92	95	83

Reporting group values	6 Through 10 Years (1 Vac)	Total	
Number of subjects	176	715	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)		0 0 0	

Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	7.8		
standard deviation	± 1.4	-	
Gender categorical			
Units: Subjects			
Female	87	356	
Male	89	359	

End points

End points reporting groups

Reporting group title	2 Through 5 Years (2 Vac)
Reporting group description: Subjects 2-5 years of age received two MenACWY-CRM vaccinations.	
Reporting group title	2 Through 5 Years (1 Vac)
Reporting group description: Subjects 2-5 years of age received one MenACWY-CRM vaccination.	
Reporting group title	6 Through 10 Years (2 Vac)
Reporting group description: Subjects 6-10 years of age received two MenACWY-CRM vaccinations.	
Reporting group title	6 Through 10 Years (1 Vac)
Reporting group description: Subjects 6-10 years of age received one MenACWY-CRM vaccination.	

Primary: Non-inferiority of Two Vaccinations Versus One Vaccination of MenACWY-CRM, by Age Cohort, as Measured by the Percentage of Subjects With hSBA Seroresponse Against N Meningitidis Serogroups A, C, W and Y, at 1 Month After Last Vaccination

End point title	Non-inferiority of Two Vaccinations Versus One Vaccination of MenACWY-CRM, by Age Cohort, as Measured by the Percentage of Subjects With hSBA Seroresponse Against N Meningitidis Serogroups A, C, W and Y, at 1 Month After Last Vaccination
End point description: Immunogenicity was measured as the percentage of subjects with overall seroresponse and associated 95% Clopper-Pearson confidence interval (CI), directed against N. meningitidis serogroups A, C, W and Y, by serum bactericidal assay using human complement (hSBA) at 1 month after one vaccination or two vaccinations of MenACWY-CRM given two months apart. Seroresponse is defined as: 1. postvaccination hSBA titer $\geq 1:8$ for subjects with a prevaccination hSBA titer $< 1:4$; 2. for subjects with a prevaccination hSBA $\geq 1:4$, an increase of at least four times of the prevaccination hSBA titer.	
End point type	Primary
End point timeframe: One Month After Last Vaccination (day 86)	

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	143	152	142
Units: Percentage of subjects				
number (confidence interval 95%)				
MenA (N=135,143,152,142)	94 (89 to 97)	75 (67 to 82)	89 (83 to 93)	77 (70 to 84)
MenC (N=131,140,149,142)	92 (86 to 96)	65 (56 to 73)	93 (87 to 96)	73 (65 to 80)
MenW (N=128,135,148,138)	75 (67 to 82)	61 (52 to 69)	58 (50 to 66)	54 (45 to 62)
MenY (N=128,133,148,142)	91 (84 to 95)	64 (55 to 72)	89 (83 to 94)	60 (51 to 68)

Statistical analyses

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenA
Statistical analysis description:	
Two vaccinations versus one vaccination of MenACWY-CRM, for 2 to 5 years of age cohort, as measured by the percentage of subjects with hSBA seroresponse against N Meningitidis serogroups A at 1 month after last vaccination.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Method	Method of Miettinen and Nurminen (MN)
Parameter estimate	Vaccine-group difference
Point estimate	19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	10
upper limit	28.9

Notes:

[1] - Noninferiority was demonstrated for 2 to 5 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenA.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenC
Statistical analysis description:	
Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup C, at 1 month after last vaccination, for age cohort 2 – 5 years of age.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	27
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	16.9
upper limit	37.7

Notes:

[2] - Noninferiority was demonstrated for 2 to 5 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenC.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenW
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup W, at 1 month after last vaccination, for age cohort 2 – 5 years of age.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	14
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.4
upper limit	26.7

Notes:

[3] - Noninferiority was demonstrated for 2 to 5 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenW.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenY
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup Y, at 1 month after last vaccination, for age cohort 2 – 5 years of age.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	27
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	15.6
upper limit	37.6

Notes:

[4] - Noninferiority was demonstrated for 2 to 5 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for Men Y.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenA
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup A, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
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Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	11
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	1.7
upper limit	21.3

Notes:

[5] - Noninferiority was demonstrated for 6 to 10 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenA.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenC
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup C, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	19
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	9.9
upper limit	29.2

Notes:

[6] - Noninferiority was demonstrated for 6 to 10 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenC.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenW
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup W, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	4

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-8.6
upper limit	17.4

Notes:

[7] - Noninferiority was demonstrated for 6 to 10 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenW.

Statistical analysis title	Non-inferiority of 2 Vac to 1 Vac, MenY
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Statistical analysis description:

Non-inferiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup Y, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	29
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	18.4
upper limit	40

Notes:

[8] - Noninferiority was demonstrated for 6 to 10 years of age group if the lower limit of the 2-sided 97.5% confidence interval (CI) for the difference in seroresponse rate between the 2-dose vaccination schedule and the 1-dose vaccination schedule (2-dose schedule minus the 1-dose schedule) was greater than -10% for MenY.

Primary: Superiority of Two Vaccinations Versus One Vaccination of MenACWY-CRM, by Age Cohort, as Measured by the Percentage of Subjects With hSBA Seroresponse Against N. Meningitidis Serogroups A, C, W and Y, at 1 Month After Last Vaccination

End point title	Superiority of Two Vaccinations Versus One Vaccination of MenACWY-CRM, by Age Cohort, as Measured by the Percentage of Subjects With hSBA Seroresponse Against N. Meningitidis Serogroups A, C, W and Y, at 1 Month After Last Vaccination
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End point description:

Immunogenicity was measured as the percentage of subjects with overall seroresponse and associated 95% CI, directed against N. meningitidis serogroups A, C, W and Y, by hSBA at 1 month after one vaccination or two vaccinations of MenACWY-CRM. Seroresponse -postvaccination hSBA titer $\geq 1:8$ for subjects with a prevaccination hSBA titer $< 1:4$ and for subjects with a prevaccination hSBA $\geq 1:4$, an increase of at least four times of the prevaccination hSBA titer.

End point type	Primary
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End point timeframe:

1 Month After Last Vaccination (day 86)

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	158	163	171	163
Units: Percentage of subjects				
number (confidence interval 95%)				
MenA (N=158,163,171,163)	95 (90 to 98)	77 (69 to 83)	89 (84 to 94)	79 (71 to 85)
MenC (N=154,157,167,162)	93 (88 to 96)	65 (57 to 72)	93 (89 to 97)	75 (68 to 82)
MenW (N=150,154,167,159)	75 (68 to 82)	61 (53 to 69)	57 (49 to 65)	52 (44 to 60)
MenY (N=150,153,167,163)	90 (84 to 94)	62 (54 to 70)	89 (83 to 93)	60 (52 to 68)

Statistical analyses

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenA
Statistical analysis description:	
Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup A, at 1 month after last vaccination, for age cohort 2 – 5 years of age.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	18
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	9.1
upper limit	28

Notes:

[9] - Superiority was demonstrated if the lower limit of the 2-sided (1-2α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenA.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenC
Statistical analysis description:	
Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup C, at 1 month after last vaccination, for age cohort 2 – 5 years of age.	
Comparison groups	2 Through 5 Years (1 Vac) v 2 Through 5 Years (2 Vac)
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	28
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	17.1
upper limit	38.7

Notes:

[10] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenC.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenW
Statistical analysis description:	
Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup W, at 1 month after last vaccination, for age cohort 2 – 5 years of age.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	14
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	1
upper limit	27.1

Notes:

[11] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenW.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenY
Statistical analysis description:	
Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup Y, at 1 month after last vaccination, for age cohort 2 – 5 years of age.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	28
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	16.2
upper limit	39.3

Notes:

[12] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenY.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenA
Statistical analysis description:	
Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup A, at 1 month after last vaccination, for age cohort 6 – 10 years of age.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	11
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	1
upper limit	21.2

Notes:

[13] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenA.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenC
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Statistical analysis description:

Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup C, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	18
Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	8.5
upper limit	28.2

Notes:

[14] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenC.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenW
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Statistical analysis description:

Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup W, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	5

Confidence interval	
level	Other: 98.75 %
sides	2-sided
lower limit	-8.4
upper limit	18.8

Notes:

[15] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenW.

Statistical analysis title	Superiority of 2 Vac to 1 Vac, MenY
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Statistical analysis description:

Superiority of two vaccinations versus one vaccination of MenACWY-CRM, as measured by the percentage of subjects with hSBA seroresponse against N. Meningitidis serogroup Y, at 1 month after last vaccination, for age cohort 6 – 10 years of age.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
Method	MN Method
Parameter estimate	Vaccine-group difference
Point estimate	29

Confidence interval

level	Other: 98.75 %
sides	2-sided
lower limit	17
upper limit	39.6

Notes:

[16] - Superiority was demonstrated if the lower limit of the 2-sided (1-2 α) % CI for seroresponse increase between the 2-dose vaccination schedule and the 1-dose vaccination schedule was above 10% for MenY.

Secondary: Percentage of Subjects With hSBA Titer \geq 1:8, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Month After One or Two Vaccination(s) of MenACWY-CRM

End point title	Percentage of Subjects With hSBA Titer \geq 1:8, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Month After One or Two Vaccination(s) of MenACWY-CRM
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End point description:

Immunogenicity was measured as the percentage of subjects who achieved hSBA titer \geq 1:8 and associated 95% CI, at one month after one vaccination or two vaccinations of MenACWY-CRM.

End point type	Secondary
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End point timeframe:

One Month After Last Vaccination (day 86)

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	143	152	142
Units: Percentage of subjects				
number (confidence interval 95%)				
MenA (N=135,143,152,142)	95 (90 to 98)	76 (68 to 82)	91 (85 to 95)	80 (73 to 86)
MenC (N=131,140,149,142)	98 (95 to 100)	76 (68 to 83)	99 (95 to 100)	89 (82 to 93)

MenW (N=128,135,148,138)	99 (96 to 100)	92 (86 to 96)	99 (96 to 100)	96 (91 to 98)
MenY (N=128,133,148,142)	96 (91 to 99)	69 (61 to 77)	96 (91 to 98)	73 (64 to 80)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Subjects, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Month After One or Two Vaccination(s) of MenACWY-CRM

End point title	Geometric Mean Titers of Subjects, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Month After One or Two Vaccination(s) of MenACWY-CRM
End point description: Immunogenicity was measured as hSBA geometric mean titers (GMTs) and 95% CI against N. meningitidis serogroups A, C, W and Y, one month after one vaccination or two vaccinations of MenACWY-CRM.	
End point type	Secondary
End point timeframe: One Month After Last Vaccination (day 86)	

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135	143	152	142
Units: Titer				
geometric mean (confidence interval 95%)				
MenA (N=135,143,152,142)	68 (54 to 86)	21 (17 to 27)	67 (52 to 87)	36 (28 to 47)
MenC (N=131,140,149,142)	146 (115 to 186)	22 (18 to 28)	165 (126 to 217)	67 (51 to 89)
MenW (N=128,135,148,138)	191 (150 to 243)	104 (83 to 132)	169 (138 to 206)	95 (78 to 117)
MenY (N=128,133,148,142)	70 (55 to 90)	15 (12 to 19)	76 (58 to 99)	26 (20 to 34)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With hSBA Titer $\geq 1:8$, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Year After One or Two Vaccination(s) of MenACWY-CRM

End point title	Percentage of Subjects With hSBA Titer $\geq 1:8$, Directed Against N. Meningitidis Serogroups A, C, W and Y At One Year After One or Two Vaccination(s) of MenACWY-CRM
End point description: Immunogenicity was measured as the percentage of subjects with hSBA titer $\geq 1:8$ and associated 95%	

CI at one year after one vaccination or two vaccinations of MenACWY-CRM.

End point type	Secondary
End point timeframe:	
One year after one vaccination or two vaccinations (day 422).	

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	131	142	130
Units: Percentage of subjects				
number (confidence interval 95%)				
MenA (N=122,131,142,130)	30 (22 to 39)	11 (6 to 17)	30 (22 to 38)	20 (14 to 28)
MenC (N=123,128,141,130)	61 (52 to 70)	41 (32 to 50)	81 (73 to 87)	55 (46 to 64)
MenW (N=121,127,139,130)	92 (85 to 96)	91 (84 to 95)	94 (89 to 97)	90 (84 to 95)
MenY (N=121,122,140,130)	67 (58 to 75)	57 (48 to 66)	75 (67 to 82)	65 (57 to 74)

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers of Subjects, Directed Against N Meningitidis Serogroups A, C, W and Y At One Year After One or Two Vaccination(s) of MenACWY-CRM

End point title	Geometric Mean Titers of Subjects, Directed Against N Meningitidis Serogroups A, C, W and Y At One Year After One or Two Vaccination(s) of MenACWY-CRM
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End point description:

Immunogenicity was measured as hSBA GMTs and 95% CI against N. meningitidis serogroups A, C, W and Y at one year after one vaccination or two vaccinations of MenACWY-CRM.

End point type	Secondary
End point timeframe:	
One year after one vaccination or two vaccinations (day 422).	

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	123	131	142	130
Units: Titer				
geometric mean (confidence interval 95%)				
MenA (N=122,131,142,130)	4.72 (3.91 to 5.71)	2.66 (2.22 to 3.19)	4.66 (3.75 to 5.81)	3.56 (2.84 to 4.46)
MenC (N=123,128,141,130)	10 (8.34 to 13)	7.03 (5.63 to 8.76)	24 (18 to 31)	15 (12 to 20)
MenW (N=121,127,139,130)	49 (39 to 62)	39 (31 to 49)	64 (52 to 79)	47 (38 to 59)
MenY (N=121,122,140,130)	14 (11 to 17)	9.88 (7.8 to 13)	20 (15 to 25)	13 (9.96 to 16)

Statistical analyses

No statistical analyses for this end point

Secondary: Numbers of 2 to 5 Years-Old Subjects Who Reported Solicited Local and Systemic Adverse Events After Any Vaccination

End point title	Numbers of 2 to 5 Years-Old Subjects Who Reported Solicited Local and Systemic Adverse Events After Any Vaccination ^[17]
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End point description:

Safety was assessed as the number of 2 to 5 years-old subjects who reported solicited local and systemic adverse events (AEs) from day 1 up to and including day 7 after one or two vaccination(s) of MenACWY-CRM.

End point type	Secondary
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End point timeframe:

From day 1 through day 7 after one or two vaccination(s)

Notes:

[17] - 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: This endpoint specifically only investigates subjects 2 through 5 years old, which means the reporting groups 6 Through 10 years (1 vac) and 6 Through 10 years (2 Vac) are out of scope.

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: Number of subjects				
Erythema (N=173,175)	25	11		
Induration (N=173,175)	19	7		
Tenderness (N=174,175)	84	79		
Change in eating habits (N=173,175)	26	30		
Sleepiness (N=173,175)	49	46		
Irritability (N=173,175)	51	50		
Body Temperature $\geq 38^{\circ}\text{C}$ (N=174,175)	9	12		

Statistical analyses

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, erythema
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Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced erythema in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
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Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	4.53

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, induration
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Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced induration in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	2.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	6.36

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, tenderness
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Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced tenderness in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.34

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, chng. eating habits
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Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced a change in eating habits in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.42

Statistical analysis title

2 Vac vs. 1 Vac, Systemic AEs, sleepiness

Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced sleepiness in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.52

Statistical analysis title

2 Vac vs. 1 Vac, Systemic AEs, irritability

Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced irritability in the two doses versus in the one dose of MenACWY.

Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.43

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, fever (≥ 38 °C)
Statistical analysis description: The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced fever (≥ 38 °C) in the two doses versus in the one dose of MenACWY.	
Comparison groups	2 Through 5 Years (2 Vac) v 2 Through 5 Years (1 Vac)
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.74

Secondary: Numbers of 6 to 10 Years-Old Subjects Who Reported Solicited Local and Systemic Adverse Events After Any Vaccination

End point title	Numbers of 6 to 10 Years-Old Subjects Who Reported Solicited Local and Systemic Adverse Events After Any Vaccination ^[18]
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End point description:

Safety was assessed as the number of 6 to 10 years-old subjects who reported solicited local and systemic adverse events from day 1 up to and including day 7 after one or two vaccination(s) of MenACWY-CRM.

End point type	Secondary
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End point timeframe:

From day 1 through day 7 after one or two vaccination(s)

Notes:

[18] - 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: This endpoint specifically only investigates subjects 6 through 10 years old, which means the reporting groups 2 Through 5 years (1 vac) and 2 Through 5 years (2 Vac) are out of scope.

End point values	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	166		
Units: Number of subjects				
Erythema (N=178,166)	23	15		
Induration (N=178,166)	24	15		
Pain (N=178,166)	106	78		
Loss of Appetite (N=177,166)	27	14		
Nausea (N=177,165)	29	21		
Fatigue (N=177,166)	44	25		
Myalgia (N=177,165)	63	43		
Arthralgia (N=177,165)	20	9		
Headache (N=177,165)	55	28		

Body Temperature $\geq 38^{\circ}\text{C}$ (N=178,166)	11	9		
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Statistical analyses

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, erythema
Statistical analysis description:	
The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced erythema in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.65

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, induration
Statistical analysis description:	
The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced induration in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.74

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, pain
Statistical analysis description:	
The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced pain in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)

Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.55

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, loss of appetite
Statistical analysis description: The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced a loss of appetite in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	3.33

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, nausea
Statistical analysis description: The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced nausea in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.17

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, fatigue
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Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced fatigue in the two doses versus in the one dose of MenACWY.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	2.57

Statistical analysis title

2 Vac vs. 1 Vac, Systemic AEs, myalgia

Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced myalgia in the two doses versus in the one dose of MenACWY.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.89

Statistical analysis title

2 Vac vs. 1 Vac, Systemic AEs, arthralgia

Statistical analysis description:

The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced arthralgia in the two doses versus in the one dose of MenACWY.

Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	4.42

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, headache
Statistical analysis description:	
The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced headache in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	2.74

Statistical analysis title	2 Vac vs. 1 Vac, Systemic AEs, fever (≥ 38 °C)
Statistical analysis description:	
The safety of two vaccine groups was compared by calculating risk ratio of the proportions of subjects who experienced fever (≥ 38 °C) in the two doses versus in the one dose of MenACWY.	
Comparison groups	6 Through 10 Years (2 Vac) v 6 Through 10 Years (1 Vac)
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.68

Secondary: Number of Subjects Who Reported Selected AEs After Any Vaccination – Day 1 to 86

End point title	Number of Subjects Who Reported Selected AEs After Any Vaccination – Day 1 to 86
End point description:	
Safety was assessed as the number subjects who reported Selected AEs from day 1 up to day 86 after one or two vaccination(s) of MenACWY.	
End point type	Secondary
End point timeframe:	
Day 1 to Day 86	

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	176 ^[19]	179	180 ^[20]	174
Units: Number of subjects				
SAEs	1	0	0	0
At least possibly related SAEs	0	0	0	0
Medically attended AEs	50	55	46	46
At least possibly related medically attended AEs	0	3	1	0
AEs resulting in premature withdrawal	0	0	0	1
Deaths	0	0	0	0

Notes:

[19] - Actual number subjects analysed in this group was 179.

[20] - Actual number subjects analysed in this group was 181.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Reported Selected AEs After Any Vaccination – Day 1 to 422

End point title	Number of Subjects Who Reported Selected AEs After Any Vaccination – Day 1 to 422
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End point description:

Safety was assessed as the number subjects who reported Selected AEs from day 1 up to day 422 after one or two vaccination(s) of MenACWY.

End point type	Secondary
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End point timeframe:

Day 1 to Day 422

End point values	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)	6 Through 10 Years (1 Vac)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	176 ^[21]	179	180 ^[22]	174
Units: Number of subjects				
SAEs	2	1	1	1
At least possibly related SAEs	0	1	0	0
Medically attended AEs	103	101	95	97
At least possibly related medically attended AEs	1	4	1	2
AEs resulting in premature withdrawal	0	0	0	1
Deaths	0	0	0	0

Notes:

[21] - Actual number subjects analysed in this group was 179.

[22] - Actual number subjects analysed in this group was 181.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs were collected day 1-day 7, unsolicited AEs were collected day 1-day 28, after each vaccination. Medically attended AEs, AEs resulting in premature withdrawal and SAEs were collected day 1-study termination.

Adverse event reporting additional description:

Solicited AEs were collected by systematic assessment; unsolicited AEs were collected by non-systematic assessment.

MedDRA version 16.1 was used for solicited and unsolicited AEs, MedDRA version 17.0 was used for selected adverse events (see outcome measure 9), and MedDRA version 17.1 was used for additional analysis of occurrence rates.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	2 Through 5 Years (2 Vac)
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Reporting group description:

Subjects 2-5 years of age received two MenACWY-CRM vaccinations.

Reporting group title	2 Through 5 Years (1 Vac)
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Reporting group description:

Subjects 2-5 years of age received one MenACWY-CRM vaccination.

Reporting group title	6 Through 10 Years (2 Vac)
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Reporting group description:

Subjects 6-10 years of age received two MenACWY-CRM vaccinations.

Reporting group title	6 Through 10 Years (1 Vac)
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Reporting group description:

Subjects 6-10 years of age received one MenACWY-CRM vaccination.

Serious adverse events	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 179 (1.12%)	1 / 179 (0.56%)	1 / 181 (0.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 181 (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
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			

subjects affected / exposed	0 / 179 (0.00%)	1 / 179 (0.56%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Intermittent explosive disorder			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oppositional defiant disorder			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 179 (0.56%)	0 / 179 (0.00%)	0 / 181 (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 / 179 (0.56%)	0 / 179 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events			
6 Through 10 Years (1 Vac)			
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 174 (0.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Intermittent explosive disorder			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oppositional defiant disorder			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Otitis media			

subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 174 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	2 Through 5 Years (2 Vac)	2 Through 5 Years (1 Vac)	6 Through 10 Years (2 Vac)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	136 / 179 (75.98%)	134 / 179 (74.86%)	142 / 181 (78.45%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 179 (3.35%)	8 / 179 (4.47%)	61 / 181 (33.70%)
occurrences (all)	9	8	96
Somnolence			
subjects affected / exposed	49 / 179 (27.37%)	47 / 179 (26.26%)	0 / 181 (0.00%)
occurrences (all)	69	60	0
General disorders and administration site conditions			
Vomiting			
subjects affected / exposed	19 / 179 (10.61%)	19 / 179 (10.61%)	15 / 181 (8.29%)
occurrences (all)	23	23	15
Fatigue			
subjects affected / exposed	1 / 179 (0.56%)	1 / 179 (0.56%)	44 / 181 (24.31%)
occurrences (all)	1	1	64
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	25 / 179 (13.97%)	11 / 179 (6.15%)	24 / 181 (13.26%)
occurrences (all)	31	12	27
Injection site induration			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	19 / 179 (10.61%) 24	7 / 179 (3.91%) 8	24 / 181 (13.26%) 27
Injection site pain alternative assessment type: Systematic			
subjects affected / exposed occurrences (all)	84 / 179 (46.93%) 116	79 / 179 (44.13%) 109	106 / 181 (58.56%) 152
Pyrexia subjects affected / exposed occurrences (all)	29 / 179 (16.20%) 38	34 / 179 (18.99%) 45	26 / 181 (14.36%) 28
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 179 (2.23%) 7	6 / 179 (3.35%) 6	5 / 181 (2.76%) 8
Diarrhoea subjects affected / exposed occurrences (all)	8 / 179 (4.47%) 10	10 / 179 (5.59%) 12	5 / 181 (2.76%) 5
Nausea subjects affected / exposed occurrences (all)	0 / 179 (0.00%) 0	0 / 179 (0.00%) 0	29 / 181 (16.02%) 41
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	22 / 179 (12.29%) 29	17 / 179 (9.50%) 21	12 / 181 (6.63%) 13
Rhinitis allergic subjects affected / exposed occurrences (all)	2 / 179 (1.12%) 2	10 / 179 (5.59%) 10	3 / 181 (1.66%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	14 / 179 (7.82%) 18	9 / 179 (5.03%) 10	3 / 181 (1.66%) 3
Psychiatric disorders			
Eating disorder subjects affected / exposed occurrences (all)	26 / 179 (14.53%) 35	30 / 179 (16.76%) 35	0 / 181 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	51 / 179 (28.49%) 78	50 / 179 (27.93%) 78	1 / 181 (0.55%) 1

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	21 / 181 (11.60%)
occurrences (all)	0	0	28
Myalgia			
subjects affected / exposed	0 / 179 (0.00%)	0 / 179 (0.00%)	64 / 181 (35.36%)
occurrences (all)	0	0	86
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	7 / 179 (3.91%)	11 / 179 (6.15%)	1 / 181 (0.55%)
occurrences (all)	8	13	1
Ear infection			
subjects affected / exposed	15 / 179 (8.38%)	6 / 179 (3.35%)	5 / 181 (2.76%)
occurrences (all)	18	8	5
Nasopharyngitis			
subjects affected / exposed	2 / 179 (1.12%)	11 / 179 (6.15%)	4 / 181 (2.21%)
occurrences (all)	2	12	4
Otitis media			
subjects affected / exposed	19 / 179 (10.61%)	24 / 179 (13.41%)	7 / 181 (3.87%)
occurrences (all)	26	34	8
Pharyngitis			
subjects affected / exposed	16 / 179 (8.94%)	16 / 179 (8.94%)	18 / 181 (9.94%)
occurrences (all)	18	18	20
Pharyngitis streptococcal			
subjects affected / exposed	12 / 179 (6.70%)	18 / 179 (10.06%)	17 / 181 (9.39%)
occurrences (all)	16	22	20
Sinusitis			
subjects affected / exposed	8 / 179 (4.47%)	12 / 179 (6.70%)	6 / 181 (3.31%)
occurrences (all)	10	18	6
Upper respiratory tract infection			
subjects affected / exposed	22 / 179 (12.29%)	21 / 179 (11.73%)	13 / 181 (7.18%)
occurrences (all)	24	31	14
Viral infection			
subjects affected / exposed	9 / 179 (5.03%)	13 / 179 (7.26%)	7 / 181 (3.87%)
occurrences (all)	15	15	8
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	1 / 179 (0.56%) 1	1 / 179 (0.56%) 1	27 / 181 (14.92%) 33
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Non-serious adverse events	6 Through 10 Years (1 Vac)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 174 (72.41%)		
Nervous system disorders			
Headache			
subjects affected / exposed	35 / 174 (20.11%)		
occurrences (all)	50		
Somnolence			
subjects affected / exposed	1 / 174 (0.57%)		
occurrences (all)	1		
General disorders and administration site conditions			
Vomiting			
subjects affected / exposed	11 / 174 (6.32%)		
occurrences (all)	11		
Fatigue			
subjects affected / exposed	25 / 174 (14.37%)		
occurrences (all)	32		
Injection site erythema			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 174 (9.20%)		
occurrences (all)	17		
Injection site induration			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 174 (9.20%)		
occurrences (all)	16		
Injection site pain			
alternative assessment type: Systematic			
subjects affected / exposed	78 / 174 (44.83%)		
occurrences (all)	109		
Pyrexia			
subjects affected / exposed	26 / 174 (14.94%)		
occurrences (all)	35		

Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	9 / 174 (5.17%) 10 5 / 174 (2.87%) 5 22 / 174 (12.64%) 25		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	15 / 174 (8.62%) 17 1 / 174 (0.57%) 1 5 / 174 (2.87%) 6		
Psychiatric disorders Eating disorder subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	0 / 174 (0.00%) 0 1 / 174 (0.57%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	12 / 174 (6.90%) 12 43 / 174 (24.71%) 54		
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	3 / 174 (1.72%)		
occurrences (all)	3		
Ear infection			
subjects affected / exposed	3 / 174 (1.72%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	4 / 174 (2.30%)		
occurrences (all)	5		
Otitis media			
subjects affected / exposed	8 / 174 (4.60%)		
occurrences (all)	9		
Pharyngitis			
subjects affected / exposed	6 / 174 (3.45%)		
occurrences (all)	7		
Pharyngitis streptococcal			
subjects affected / exposed	14 / 174 (8.05%)		
occurrences (all)	19		
Sinusitis			
subjects affected / exposed	8 / 174 (4.60%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	16 / 174 (9.20%)		
occurrences (all)	18		
Viral infection			
subjects affected / exposed	4 / 174 (2.30%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 174 (8.05%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2012	The study design was revised and the study became a two-stage study. The procedures for safety follow-up have been changed, as well as the safety and immunological statistical evaluation procedures.
03 October 2012	Main changes: a safety phone call was introduced at 180 days after Visit 2; an inclusion criterion was changed; the delegation of duties was changed; the text of the primary endpoint, secondary endpoints, and analysis of safety (endpoints) and tolerability was edited to align with the statistical analysis plan and the clinical study report shell; a section on data collection and source documents was added; and the laboratory procedures were updated.
07 June 2013	Main changes: the text on the success criteria, statistical hypotheses and sequential testing, sample size calculations was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported