Clinical trial results:
A Phase 2, Open Label, Multi-Center, Controlled, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine +/- OMV, when Administered to Healthy Infants at 2, 4, 6 and/or 12 Months of Age.

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

Summary

EudraCT number	2006-001522-84
Trial protocol	GB
Global end of trial date	15 August 2008

Results information

Result version number	v2 (current)
This version publication date	16 June 2016
First version publication date	27 November 2014
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	V72P6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00381615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Vaccines and Diagnostics S.r.l.
Sponsor organisation address	Via Fiorentina, 1, Siena, Italy, 53100
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000139-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the immunogenicity of Novartis rMenB Vaccine +/- OMV-NZ when administered to healthy infants at 2, 4 and 6 months of age, at 30 days after the third dose, by evaluation of the breadth of bactericidal activity (BCA) response against a panel of genetically distinct meningococcal strains.
To explore the safety and tolerability of the study and concomitant vaccines in all study subjects.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, GCP according to International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirement(s) for the country in which the trial was conducted, and applicable Standard Operating Procedures (SOPs). Specifically, this trial was conducted by scientifically and medically qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 147
Worldwide total number of subjects	147
EEA total number of subjects	147

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)	147
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 3 study centres in UK

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

Arms

Are arms mutually exclusive?	Yes
Arm title	rMenB

Arm description:

Infants received 4 doses of rMenB vaccine without OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Arm type	Experimental
Investigational medicinal product name	rMenB
Investigational medicinal product code	
Other name	Recombinant MenB second generation, Recombinant Neisseria meningitidis group B NHBA fusion protein, Recombinant Neisseria meningitidis group B NadA protein.
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

4 doses of 0.5 mL each

Arm title	rMenB+OMV

Arm description:

Infants received 4 doses of rMenB vaccine with OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib- IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Arm type	Experimental
Investigational medicinal product name	rMenB+OMV NZ
Investigational medicinal product code	
Other name	Recombinant MenB second generation with outer membrane vesicles (OMV) derived from the N. meningitidis serogroup B strain NZ98/254 (OMV NZ), 4CMenB, Bexsero.
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

4 doses of 0.5 mL each

Arm title	Routine

Arm description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine without OMV NZ

at 12 months of age.

Arm type	Experimental
Investigational medicinal product name	rMenB
Investigational medicinal product code	
Other name	Recombinant MenB second generation, Recombinant Neisseria meningitidis group B NHBA fusion protein, Recombinant Neisseria meningitidis group B NadA protein.
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

4 doses of 0.5 mL each

Arm title	Routine+OMV

Arm description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine with OMV NZ at 12 months of age.

Arm type	Experimental
Investigational medicinal product name	rMenB+OMV NZ
Investigational medicinal product code	
Other name	Recombinant MenB second generation with outer membrane vesicles OMV derived from the N. meningitidis serogroup B strain NZ98/254 (OMV NZ), 4CMenB, Bexsero.
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 dose of 0.5 mL each

Number of subjects in period 1	rMenB	rMenB+OMV	Routine
Started	48	50	25
Completed	44	45	24
Not completed	4	5	1
Consent withdrawn by subject	1	3	-
Lost to follow-up	3	2	-
Protocol deviation	-	-	1

Number of subjects in period 1	Routine+OMV
Started	24
Completed	22
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	rMenB
Reporting group description:	
Infants received 4 doses of rMenB vaccine without OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).	
Reporting group title	rMenB+OMV
Reporting group description:	
Infants received 4 doses of rMenB vaccine with OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib- IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).	
Reporting group title	Routine
Reporting group description:	
Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine without OMV NZ at 12 months of age.	
Reporting group title	Routine+OMV
Reporting group description:	
Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine with OMV NZ at 12 months of age.	

Reporting group values	rMenB	rMenB+OMV	Routine
Number of subjects	48	50	25
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	59	60.9	60.4
standard deviation	± 3.4	± 5.9	± 5.9
Gender categorical Units: Subjects			
Female	24	22	9
Male	24	28	16

Reporting group values	Routine+OMV	Total	
Number of subjects	24	147	
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	60.9		
standard deviation	± 6.1	-	

Gender categorical Units: Subjects			
Female	7	62	
Male	17	85	

Subject analysis sets

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

Subject analysis set description:

All subjects who have data in the demographic panel

Subject analysis set title	Per Protocol Population 1 month after 2nd inj (PP Post 2nd)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first and second dose of rMenB±OMV vaccines (groups I and II), provided evaluable serum samples at the relevant time points at least until one month after second injection, and had no major protocol violation as defined prior to analysis

Subject analysis set title	Per Protocol Population 1 month after 3rd inj (PP Post 3rd)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first, second and third rMenB±OMV vaccines (groups I and II), provided evaluable serum samples at the relevant time points at least until one month after third injection, and had no major protocol violation as defined prior to analysis

Subject analysis set title	PP (Per Protocol) Post-Booster or 1st Vacc
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first, second, third and fourth (booster) rMenB±OMV vaccinations (groups I and II) and who received first vaccination (Routine±OMV groups, III and IV), provided evaluable serum samples at all relevant time points, and had no major protocol violation as defined prior to analysis

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

Subject analysis set description:

All enrolled subjects who actually received a study vaccination and provided post-baseline safety data

Reporting group values	All Enrolled Population	Per Protocol Population 1 month after 2nd inj (PP Post 2nd)	Per Protocol Population 1 month after 3rd inj (PP Post 3rd)
Number of subjects	147	79	77
Age categorical Units: Subjects			
Age continuous Units: days			
arithmetic mean	60.2		
standard deviation	± 5.3	±	±
Gender categorical Units: Subjects			
Female	62		
Male	85		

Reporting group values	PP (Per Protocol) Post-Booster or 1st Vacc	Safety Population	

Number of subjects	112	147	
Age categorical Units: Subjects			

Age continuous Units: days arithmetic mean standard deviation	± 	± 	
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	rMenB

Reporting group description:

Infants received 4 doses of rMenB vaccine without OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Reporting group title	rMenB+OMV

Reporting group description:

Infants received 4 doses of rMenB vaccine with OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib- IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Reporting group title	Routine

Reporting group description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine without OMV NZ at 12 months of age.

Reporting group title	Routine+OMV

Reporting group description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine with OMV NZ at 12 months of age.

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

Subject analysis set description:

All subjects who have data in the demographic panel

Subject analysis set title	Per Protocol Population 1 month after 2nd inj (PP Post 2nd)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first and second dose of rMenB±OMV vaccines (groups I and II), provided evaluable serum samples at the relevant time points at least until one month after second injection, and had no major protocol violation as defined prior to analysis

Subject analysis set title	Per Protocol Population 1 month after 3rd inj (PP Post 3rd)
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first, second and third rMenB±OMV vaccines (groups I and II), provided evaluable serum samples at the relevant time points at least until one month after third injection, and had no major protocol violation as defined prior to analysis

Subject analysis set title	PP (Per Protocol) Post-Booster or 1st Vacc
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects in the enrolled population who received first, second, third and fourth (booster) rMenB±OMV vaccinations (groups I and II) and who received first vaccination (Routine±OMV groups, III and IV), provided evaluable serum samples at all relevant time points, and had no major protocol violation as defined prior to analysis

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

Subject analysis set description:

All enrolled subjects who actually received a study vaccination and provided post-baseline safety data

Primary: Percentages of subjects with bactericidal titers, BCA ≥1:4, 30 days after the third immunization

End point title	Percentages of subjects with bactericidal titers, BCA ≥1:4, 30 days after the third immunization[1][2]

End point description:

Percentages of subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) with a bactericidal activity (BCA) measured as BCA titer ≥1:4 for three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) at 30 days after the third immunization. The analysis was done on the Per Protocol population at one month after third injection.

End point type	Primary

End point timeframe:

At baseline (pre-vaccination) and 30 days after the third vaccination

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: 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	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain 44/76-SL (Pre-Vaccination; N=45, 45)	11 (4 to 24)	11 (4 to 24)		
Strain 5/99 (Pre-Vaccination; N=42,43)	7 (1 to 19)	14 (5 to 28)		
Strain NZ98/254 Pre-Vaccination	4 (1 to 15)	9 (2 to 21)		
Strain 44/76-SL (1 Month After 3rd Vacc; N=36, 39)	78 (61 to 90)	87 (73 to 96)		
Strain 5/99 (1 Month After 3rd Vacc; N=32, 37)	100 (89 to 100)	95 (82 to 99)		
Strain NZ98/254 (1 Month After 3rd Vacc; N=37, 40)	5 (1 to 18)	85 (70 to 94)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers against a panel of genetically distinct meningococcal strains 30 days after the third immunization

End point title	Geometric Mean Titers against a panel of genetically distinct meningococcal strains 30 days after the third immunization[3][4]

End point description:

Geometric Mean Titers (GMTs) as measure of the bactericidal activity against the for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) in subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) at 30 days after the third immunization. The analysis was done on the Per Protocol population at one month after third injection.

End point type	Primary

End point timeframe:

At baseline (pre-vaccination) and 30 days after the third vaccination

Notes:

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

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

End point values	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Titers				
geometric mean (confidence interval 95%)				
Strain 44/76-SL (Pre-Vaccination; N=45, 45)	1.32 (1.05 to 1.66)	1.4 (1.16 to 1.69)		
Strain 5/99 (Pre-Vaccination; N=42, 43)	1.22 (0.98 to 1.52)	1.43 (1.12 to 1.81)		
Strain NZ98/254 Pre-Vaccination	1.23 (1 to 1.52)	1.15 (1.02 to 1.29)		
Strain 44/76-SL (1 Month After 3rd Vacc; N=36, 39)	13 (8.11 to 22)	30 (19 to 46)		
Strain 5/99 (1 Month After 3rd Vacc; 32, 37)	159 (100 to 253)	126 (77 to 205)		
Strain NZ98/254 (1 Month After 3rd Vac; N=37, 40)	1.16 (0.98 to 1.38)	19 (11 to 33)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentages of subjects with fourfold rises in bactericidal titers after the third immunization

End point title	Percentages of subjects with fourfold rises in bactericidal titers after the third immunization[5][6]

End point description:

Percentages of subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) with fourfold rises in bactericidal titers for three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) at 30 days after the third immunization. The analysis was done on the Per Protocol population at one month after third injection.

End point type	Primary

End point timeframe:

30 days after the third vaccination

Notes:

[5] - 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.

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

End point values	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Percentage of subjects				
number (confidence interval 95%)				
Strain 44/76-SL (1 Month After 3rd Vacc; N=36, 39)	69 (52 to 84)	85 (69 to 94)		
Strain 5/99 (1 Month After 3rd Vacc; N=32,37)	97 (84 to 100)	92 (78 to 98)		
Strain NZ98/254 (1 Month After 3rd Vacc; N=37,40)	3 (0.068 to 14)	78 (62 to 89)		

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Ratios to baseline against a panel of genetically distinct meningococcal strains 30 days after the third immunization

End point title	Geometric Mean Ratios to baseline against a panel of genetically distinct meningococcal strains 30 days after the third immunization[7][8]

End point description:

Geometric Mean Ratios (GMRs) as measure of the bactericidal activity against the for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) in subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) at 30 days after the third immunization. The analysis was done on the Per Protocol population at one month after third injection.

End point type	Primary

End point timeframe:

At baseline (pre-vaccination) and 30 days after the third vaccination

Notes:

[7] - 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.

[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	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: Ratio				
geometric mean (confidence interval 95%)				
Strain 44/76-SL (1 Month After 3rd Vacc; N=36, 39)	9.89 (5.79 to 17)	21 (13 to 34)		
Strain 5/99 (1 Month After 3rd Vacc; N=32, 37)	131 (78 to 220)	91 (53 to 158)		
Strain NZ98/254 (1 Month After 3rd Vacc; N=37, 40)	0.91 (0.67 to 1.25)	16 (9.4 to 28)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting solicited local reactions during the 7 days following each vaccination of rMenB vaccine with and without OMV

End point title	Number of subjects reporting solicited local reactions during the 7 days following each vaccination of rMenB vaccine with and without OMV[9]

End point description:

Safety was assessed as the number of subjects who reported solicited local reactions from day 1 through day 7 after each vaccination of rMenB vaccine with and without OMV administered at 2 months (injection 1), 4 months (injection 3), 6 months (injection 5) and 12 months (injection 6; injection 5 for Routine and Routine+OMV groups). Analysis performed on the safety set, i.e. the subjects in the exposed population who provided post-vaccination safety data.

End point type	Primary

End point timeframe:

Day 1 through day 7 after each vaccination

Notes:

[9] - 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: All safety analyses were run in the safety population.

End point values	rMenB	rMenB+OMV	Routine	Routine+OMV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	50	24	23
Units: Subjects				
Tenderness (injection 1; N=48, 50, 0, 0)	17	17	0	0
Tenderness (injection 3; N=48, 48, 0, 0)	10	14	0	0
Tenderness (injection 5; N=47, 48, 24, 23)	10	17	6	7
Tenderness (injection 6; N=45, 48, 0, 0)	10	23	0	0
Erythema (injection 1; N=48, 50, 0, 0)	40	42	0	0
Erythema (injection 3; N=48, 48, 0, 0)	43	45	0	0
Erythema (injection 5; N=47, 48, 24, 23)	43	44	22	23
Erythema (injection 6; N=45, 48, 0, 0)	43	46	0	0
Induration (injection 1; N=48, 50, 0, 0)	15	24	0	0
Induration (injection 3; N=48, 48, 0, 0)	13	24	0	0
Induration (injection 5; N=47, 48, 24, 23)	20	22	10	19
Induration (injection 6; N=45, 48, 0, 0)	22	34	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting solicited local reactions during the 7 days following each vaccination of PC7

End point title	Number of subjects reporting solicited local reactions during the 7 days following each vaccination of PC7[10]

End point description:

Safety was assessed as the number of subjects who reported solicited local reactions from day 1 through day 7 after each vaccination of PC7 administered at 2 months (injection 1) and 4 months (injection 3). Analysis performed on the safety set, i.e. the subjects in the exposed population who provided post-vaccination safety data.

End point type	Primary

End point timeframe:

Day 1 through day 7 after each vaccination

Notes:

[10] - 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: All safety analyses were run in the safety population.

End point values	rMenB	rMenB+OMV	Routine	Routine+OMV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	50	25	24
Units: Subjects				
Tenderness (injection 1; N=48, 50, 25, 24)	19	21	7	10
Tenderness (injection 3; N=48, 48, 25, 24)	10	12	6	6
Erythema (injection 1; N=48, 50, 25, 24)	38	43	24	20
Erythema (injection 3; N=48, 48, 25, 24)	43	42	24	22
Induration (injection 1; N=48, 50, 25, 24)	19	21	11	13
Induration (injection 3; N=48, 48, 25, 24)	19	19	13	16

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting solicited local reactions during the 7 days following each vaccination of DTaP-Hib-IPV Pentavalent Vaccine

End point title	Number of subjects reporting solicited local reactions during the 7 days following each vaccination of DTaP-Hib-IPV Pentavalent Vaccine[11]

End point description:

Safety was assessed as the number of subjects who reported solicited local reactions from day 1 through day 7 after each vaccination of the pentavalent vaccine DTaP-Hib-IPV administered at 2 months (injection 1), 3 months (injection 2) and 4 months (injection 3). Analysis performed on the safety set, i.e. the subjects in the exposed population who provided post-vaccination safety data.

End point type	Primary

End point timeframe:

Day 1 through day 7 after each vaccination

Notes:

[11] - 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: All safety analyses were run in the safety population.

End point values	rMenB	rMenB+OMV	Routine	Routine+OMV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	50	25	24
Units: Subjects				
Tenderness (injection 1; N=48, 50, 25, 24)	21	22	8	14
Tenderness (injection 2; N=48, 49, 25, 24)	14	8	5	5
Tenderness (injection 3; N=48, 48, 25, 24)	12	12	3	6
Erythema (injection 1; N=48, 50, 25, 24)	37	41	24	22
Erythema (injection 2; N=48, 49, 25, 24)	42	44	25	22
Erythema (injection 3; N=48, 48, 25, 24)	41	42	24	23
Induration (injection 1; N=48, 50, 25, 24)	19	20	10	16
Induration (injection 2; N=48, 49, 25, 24)	17	16	8	11
Induration (injection 3; N=48, 48, 25, 24)	23	20	13	15

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting solicited local reactions during the 7 days following each vaccination of MCC or MCC-Hib administered at 2 and 5 months. MenC-Hib was administered at 12 months of age

End point title	Number of subjects reporting solicited local reactions during the 7 days following each vaccination of MCC or MCC-Hib administered at 2 and 5 months. MenC-Hib was administered at 12 months of age[12]

End point description:

Safety was assessed as the number of subjects who reported solicited local reactions from day 1 through day 7 after each vaccination of MCC or MCC-Hib administered at 2 months (injection 2), 5 months (injection 4) and 12 months (injection 6 for rMenB±OMV NZ and injection 5 for Routine and Routine+OMV groups). Analysis performed on the safety set, i.e. the subjects in the exposed population who provided post-vaccination safety data.

End point type	Primary

End point timeframe:

Day 1 through day 7 after each vaccination

Notes:

[12] - 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: All safety analyses were run in the safety population.

End point values	rMenB	rMenB+OMV	Routine	Routine+OMV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	49	25	24
Units: Subjects				
Tenderness (injection 2)	7	8	7	5

Tenderness (injection 4; N=48, 48, 25, 24)	7	10	3	6
Tenderness (injection 5; N=0, 0, 24, 23)	0	0	5	5
Tenderness (injection 6; N=45, 48, 0, 0)	8	15	0	0
Erythema (injection 2)	37	44	24	21
Erythema (injection 4; N=48, 48, 25, 24)	42	43	21	21
Erythema (injection 5; N=0, 0, 24, 23)	0	0	22	23
Erythema (injection 6; N=45, 48, 0, 0)	44	45	0	0
Induration (injection 2)	12	16	10	7
Induration (injection 4; N=48, 48, 25, 24)	13	21	11	11
Induration (injection 5; N=0, 0, 24, 23)	0	0	12	16
Induration (injection 6; N=45, 48, 0, 0)	21	24	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects who reported solicited systemic reactions and other indicator of reactogenicity after each vaccination administered during study

End point title	Number of subjects who reported solicited systemic reactions and other indicator of reactogenicity after each vaccination administered during study[13]

End point description:

Safety was assessed as the number of subjects who reported solicited systemic reactions and other indicator of reactogenicity from day 1 through day 7 after each vaccination administered during study as follow: rMenB vaccine with and without OMV, PC7, DTaP-Hib-IPV at 2 months (injection 1), MenC-CRM, DTaP-Hib-IPV at 3 months (injection 2), rMenB vaccine with and without OMV, PC7, DTaP-Hib-IPV at 4 months (injection 3), MenC-CRM at 5 months (injection 4), rMenB vaccine with and without OMV at 6 months (injection 5; rMenB and rMenB+OMV groups only), rMenB vaccine with and without OMV +MCC-Hib at 12 months (injection 5; routine and routine+OMV groups only), rMenB vaccine with and without OMV +MCC-Hib (injection 6; rMenB and rMenB+OMV groups only). Analysis performed on the safety set, i.e. the subjects in the exposed population who provided post-vaccination safety data.

End point type	Primary

End point timeframe:

Day 1 through day 7 after each vaccination

Notes:

[13] - 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: All safety analyses were run in the safety population.

End point values	rMenB	rMenB+OMV	Routine	Routine+OMV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	50	25	24
Units: Subjects				
Change Eat. Habits (injection 1)	7	13	11	5
Change Eat. Habits (injection 2; N=48, 49, 25, 24)	4	6	3	1
Change Eat. Habits (injection 3; N=48, 48, 25, 24)	12	9	3	4
Change Eat. Habits (injection 4; N=48, 48, 25, 24)	3	3	1	1

Change Eat. Habits (injection 5; N=47, 48, 24, 23)	7	14	6	6
Change Eat. Habits (injection 6; N=45, 48, 0, 0)	11	13	0	0
Sleepiness (injection 1)	32	32	19	15
Sleepiness (injection 2; N=48, 49, 25, 24)	19	17	12	9
Sleepiness (injection 3; N=48, 48, 25, 24)	15	21	6	7
Sleepiness (injection 4; N=48, 48, 25, 24)	5	7	6	3
Sleepiness (injection 5; N=47, 48, 24, 23)	5	20	5	10
Sleepiness (injection 6; N=45, 48, 0, 0)	4	13	0	0
Vomiting (injection 1)	9	3	7	5
Vomiting (injection 2; N=48, 49, 25, 24)	4	1	5	2
Vomiting (injection 3; N=48, 48, 25, 24)	3	5	1	1
Vomiting (injection 4; N=48, 48, 25, 24)	3	1	1	2
Vomiting (injection 5; N=47, 48, 24, 23)	6	5	1	3
Vomiting (injection 6; N=45, 48, 0, 0)	4	3	0	0
Diarrhea (injection 1)	13	5	4	7
Diarrhea (injection 2; N=48, 49, 25, 24)	7	5	4	3
Diarrhea (injection 3; N=48, 48, 25, 24)	8	5	3	4
Diarrhea (injection 4; N=48, 48, 25, 24)	5	2	3	3
Diarrhea (injection 5; N=47, 48, 24, 23)	1	4	1	1
Diarrhea (injection 6; N=45, 48, 0, 0)	7	5	0	0
Irritability (injection 1)	34	37	17	15
Irritability (injection 2; N=48, 49, 25, 24)	26	29	14	13
Irritability (injection 3; N=48, 48, 25, 24)	27	34	13	12
Irritability (injection 4; N=48, 48, 25, 24)	15	15	7	6
Irritability (injection 5; N=47, 48, 24, 23)	17	30	10	13
Irritability (injection 6; N=45, 48, 0, 0)	20	30	0	0
Unusual Crying (injection 1)	11	9	8	7
Unusual Crying (injection 2; N=48, 49, 25, 24)	7	6	5	1
Unusual Crying (injection 3; N=48, 48, 25, 24)	11	7	9	6
Unusual Crying (injection 4; N=48, 48, 25, 24)	5	3	3	2
Unusual Crying (injection 5; N=47, 48, 24, 23)	3	10	3	4
Unusual Crying (injection 6; N=45, 48, 0, 0)	3	5	0	0
Rash (injection 1)	10	2	2	3
Rash (injection 2; N=48, 49, 25, 24)	6	3	3	2
Rash (injection 3; N=48, 48, 25, 24)	7	5	0	2
Rash (injection 4; N=48, 48, 25, 24)	9	4	3	4
Rash (injection 5; N=47, 48, 24, 23)	7	7	5	1
Rash (injection 6; N=45, 48, 0, 0)	6	8	0	0

Fever (≥38C) (injection 1; N=48, 50, 25, 23)	1	9	0	1
Fever (≥38C) (injection 2; N=48, 49, 25, 24)	0	0	1	1
Fever (≥38C) (injection 3; N=48, 48, 25, 24)	3	4	2	0
Fever (≥38C) (injection 4; N=48, 48, 25, 24)	3	0	2	1
Fever (≥38C) (injection 5; N=47, 48, 24, 23)	1	2	4	4
Fever (≥38C) (injection 6; N=45, 48, 0, 0)	3	3	0	0
Analg. Antipyr. Med. Used (inj1)	15	29	10	8
Analg. Antipyr. Med. Used (inj2; N=48, 49, 25, 24)	15	23	10	8
Analg. Antipyr. Med. Used (inj3; N=48, 48, 25, 24)	23	31	14	10
Analg. Antipyr. Med. Used (inj4; N=48, 48, 25, 24)	10	17	3	9
Analg. Antipyr. Med. Used (inj5; N=47, 48, 24, 23)	15	30	9	13
Analg. Antipyr. Med. Used (inj6; N=45, 48, 0, 0)	16	33	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratios (GMRs) to baseline against a panel of genetically distinct meningococcal strains 30 days after the second immunization and 1 month after fourth (booster) vaccination

End point title	Geometric Mean Ratios (GMRs) to baseline against a panel of genetically distinct meningococcal strains 30 days after the second immunization and 1 month after fourth (booster) vaccination[14]

End point description:

Geometric Mean Ratios (GMRs) to baseline as measure of the bactericidal activity against for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) in subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) at 30 days after the second immunization and 1 month after fourth (booster) vaccination. The analysis was done on the Per Protocol population at 30 days after the second immunization and 1 month after fourth (booster) vaccination.

End point type	Secondary

End point timeframe:

30 days after the second vaccination and 1 month after fourth (booster) vaccination

Notes:

[14] - 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	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	38		
Units: Ratio				
geometric mean (confidence interval 95%)				
Strain 44/76-SL (1 Month After 2nd Vacc; N=40, 37)	4.36 (2.78 to 6.84)	19 (13 to 29)		
Strain 5/99 (1 Month After 2nd Vacc; N=36, 33)	104 (54 to 200)	71 (44 to 115)		
Strain NZ98/254 (1 Month After 2nd Vacc; N=41, 38)	0.92 (0.69 to 1.22)	5.55 (3.9 to 7.92)		
44/76-SL (1 month after booster; N=38, 31)	42 (28 to 64)	78 (47 to 130)		
5/99 (1 month after booster; N=34, 30)	217 (128 to 370)	467 (231 to 945)		
NZ98/254 (1 month after booster; N=39, 31)	0.85 (0.62 to 1.16)	28 (15 to 52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of subjects with Bactericidal titers, BCA, ≥1:4 after the second immunization and at 12 months age

End point title	Percentages of subjects with Bactericidal titers, BCA, ≥1:4 after the second immunization and at 12 months age[15]

End point description:

Percentages of subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) with a bactericidal activity (BCA) measured as BCA titer ≥1:4 for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) at 30 days after the second vaccination and at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination. The analysis was done on the Per Protocol population at 30 days after the second vaccination and at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination.

End point type	Secondary

End point timeframe:

At baseline (pre-vaccination) and 30 days after the second vaccination and at 12 months age.

Notes:

[15] - 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	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain 44/76-SL (Pre-Vaccination; N=45, 45)	11 (4 to 24)	11 (4 to 24)		
Strain 5/99 (Pre-vaccination; N=42, 43)	7 (1 to 19)	14 (5 to 28)		
Strain NZ98/254 Pre-Vaccination	4 (1 to 15)	9 (2 to 11)		

Strain 44/76-SL (1 Month After 2nd Vacc; N=40, 37)	58 (41 to 73)	95 (82 to 99)		
Strain 5/99 (1 Month After 2nd Vacc; N=36, 33)	89 (74 to 97)	100 (89 to 100)		
Strain NZ98/254 (1 Month After 2nd Vacc; N=41, 38)	5 (1 to 17)	74 (57 to 87)		
44/76-SL (6 months after pre-booster; N=40, 44)	70 (53 to 83)	68 (52 to 81)		
Strain 5/99 (6 months after pre-booster; N=37, 40)	92 (78 to 98)	88 (73 to 96)		
NZ98/254 (6 months after pre-booster; N=41, 44)	5 (1 to 17)	36 (22 to 52)		
44/76-SL (1 month after booster; N=38, 31)	100 (91 to 100)	100 (89 to 100)		
5/99 (1 month after booster; N=34, 30)	97 (85 to 100)	97 (83 to 100)		
NZ98/254 (1 month after booster; N=39, 31)	3 (0.065 to 13)	94 (79 to 99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of subjects with fourfold rises in bactericidal titers after the second immunization and at 12 months age

End point title	Percentages of subjects with fourfold rises in bactericidal titers after the second immunization and at 12 months age[16]

End point description:

Percentages of subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) with fourfold rises in bactericidal titers for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) at 30 days after the second vaccination and at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination. The analysis was done on the Per Protocol population 30 days after the second vaccination and at 12 months age.

End point type	Secondary

End point timeframe:

At baseline (pre-vaccination) and 30 days after the second vaccination and at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination.

Notes:

[16] - 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	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Strain 44/76-SL (1 Month After 2nd Vacc; N=40, 37)	50 (34 to 66)	86 (71 to 95)		
Strain 5/99 (1 Month After 2nd Vacc; N=36, 33)	89 (74 to 97)	94 (80 to 99)		
Strain NZ98/254 (1 Month After 2nd Vacc; N=41, 38)	2 (0.062 to 13)	55 (38 to 71)		
44/76-SL (6 months after pre-booster; N=40, 44)	45 (29 to 62)	41 (26 to 57)		

5/99 (6 months after pre-booster; N=37, 40)	84 (68 to 94)	65 (48 to 79)		
NZ98/254 (6 months after pre-booster; N=41, 44)	2 (0.062 to 13)	23 (11 to 38)		
44/76-SL (1 month after 4th (booster); N=37, 30)	92 (78 to 98)	93 (78 to 99)		
5/99 (1 month after 4th (booster); N=33, 27)	95 (85 to 100)	97 (83 to 100)		
NZ98/254 (1 month after 4th (booster); N=38, 29)	0 (0 to 9)	76 (56 to 90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers against a panel of genetically distinct meningococcal strains prior to the first dose, 30 days after the second immunization and at 12 months age

End point title	Geometric Mean Titers against a panel of genetically distinct meningococcal strains prior to the first dose, 30 days after the second immunization and at 12 months age[17]

End point description:

Geometric Mean Titers (GMTs) as measure of the bactericidal activity against the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) in subjects treated with Novartis rMenB Vaccine +/- OMV NZ (Groups I and II) prior to the first dose, at 30 days after the second immunization, at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination. The analysis was done on the Per Protocol population 30 days after the second vaccination and at 12 months age.

End point type	Secondary

End point timeframe:

prior to the first dose, 30 days after the second vaccination and at 12 months age, i.e. 6 months after third (pre-booster) vaccination, and 1 month after fourth (booster) vaccination

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

End point values	rMenB	rMenB+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: Titers				
geometric mean (confidence interval 95%)				
Strain 44/76-SL (pre-vaccination; N=45, 45)	1.32 (1.05 to 1.66)	1.4 (1.16 to 1.69)		
Strain 5/99 (pre-vaccination; N=42, 43)	1.22 (0.98 to 1.52)	1.43 (1.12 to 1.81)		
Strain NZ98/254 (pre-vaccination)	1.23 (1 to 1.52)	1.15 (1.02 to 1.29)		
Strain 44/76-SL (1 Month After 2nd Vacc; N=40, 37)	5.96 (3.94 to 9.01)	28 (19 to 40)		
Strain 5/99 (1 Month After 2nd Vacc; N=36, 33)	119 (63 to 223)	104 (64 to 169)		
Strain NZ98/254 (1 Month After 2nd Vacc; N=41, 38)	1.13 (0.97 to 1.31)	6.55 (4.77 to 8.99)		

44/76-SL (6 months after pre-booster; N=40, 44)	5.46 (4.06 to 7.35)	5.07 (3.62 to 7.1)		
5/99 (6 months after pre-booster; N=37, 40)	37 (23 to 61)	21 (13 to 37)		
NZ98/254 (6 months after pre-booster; N=41, 44)	1.14 (0.95 to 1.38)	2.38 (1.65 to 3.43)		
44/76-SL (1 month after booster; N=38, 31)	56 (40 to 79)	114 (76 to 173)		
5/99 (1 month after booster; N=34, 30)	261 (157 to 435)	691 (357 to 1340)		
NZ98/254 (1 month after booster; N=39, 31)	1.09 (0.91 to 1.31)	33 (17 to 61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with Bactericidal titers ≥1:4 at 12 months age

End point title	Percentages of Subjects with Bactericidal titers ≥1:4 at 12 months age[18]

End point description:

Percentages of subjects treated with Routine + Novartis rMenB Vaccine +/- OMV NZ (Groups III and IV) with a bactericidal activity (BCA) measured as BCA titer ≥1:4 for the for three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) at 12 months age, i.e. pre-first vaccination, and 1 month after first vaccination. The analysis was done on the Per Protocol population at 12 months age, i.e. pre-first vaccination, and 1 month after first vaccination.

End point type	Secondary

End point timeframe:

pre-first vaccination and 1 month after first vaccination

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

End point values	Routine	Routine+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Subjects				
geometric mean (confidence interval 95%)				
44/76-SL (12 Months Age, pre-first vacc; N=22, 22)	9 (1 to 29)	18 (5 to 40)		
5/99 (12 Months of Age, pre-first vacc; N=21, 22)	32 (14 to 55)	73 (50 to 89)		
NZ98/254 (12 Months Age, pre-first vacc; N=21, 22)	0 (0 to 16)	0 (0 to 15)		
44/76-SL (1 month after first Vacc; N=22, 22)	100 (84 to 100)	73 (50 to 89)		
5/99 (1 month after first Vacc; N=21, 22)	0 (0 to 16)	0 (0 to 15)		
NZ98/254 (1 month after first Vacc; N=21, 22)	0 (0 to 16)	18 (5 to 40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with fourfold rises in bactericidal titers 1 month after first vaccination

End point title	Percentages of Subjects with fourfold rises in bactericidal titers 1 month after first vaccination[19]

End point description:

Percentages of subjects treated with Routine + Novartis rMenB Vaccine +/- OMV NZ (Groups III and IV) with fourfold rises in bactericidal titers for the three major meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) 1 month after first vaccination. The analysis was done on the Per Protocol population 1 month after first vaccination.

End point type	Secondary

End point timeframe:

1 month after first vaccination

Notes:

[19] - 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	Routine	Routine+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Percentage of Subjects				
number (confidence interval 95%)				
44/76-SL (1 month after first Vacc; N=22, 22)	14 (3 to 35)	36 (17 to 59)		
5/99 (1 month after first Vacc; N=21, 22)	100 (84 to 100)	59 (36 to 79)		
NZ98/254 (1 month after first Vacc; N=21, 22)	0 (0 to 16)	9 (1 to 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Titers against a panel of genetically distinct meningococcal strains prior to and 30 days after a single dose administered at 12 months of age

End point title	Geometric Mean Titers against a panel of genetically distinct meningococcal strains prior to and 30 days after a single dose administered at 12 months of age[20]

End point description:

Geometric Mean Titers (GMTs) as measure of the bactericidal activity against the for the three major

meningococcal B strains (Strain 44/76-SL, Strain 5/99, Strain NZ98/254) in subjects treated with Routine +Novartis rMenB Vaccine +/- OMV NZ (Groups III and IV) at 12 months age, i.e. pre-first vaccination and 1 month after first vaccination. The analysis was done on the Per Protocol population.

End point type	Secondary

End point timeframe:

pre-first vaccination and 1 month after first vaccination

Notes:

[20] - 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	Routine	Routine+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Titers				
geometric mean (confidence interval 95%)				
44/76-SL (pre-vaccination; N=22, 22)	1.55 (1.22 to 1.98)	1.88 (1.19 to 2.96)		
5/99 (pre-vaccination; N=21, 22)	1 (1 to 1)	1 (1 to 1)		
NZ98/254 (pre-vaccination; N=21, 22)	1.03 (0.96 to 1.11)	1 (1 to 1)		
44/76-SL (1 month after first Vacc; N=22, 22)	2.34 (1.66 to 3.29)	6.02 (3.5 to 10)		
5/99 (1 month after first Vacc; N=21, 22)	73 (53 to 101)	8 (4.2 to 15)		
NZ98/254 (1 month after first Vacc; N=21, 22)	1 (1 to 1)	1.66 (1.12 to 2.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratios to baseline against a panel of genetically distinct meningococcal strains 30 days after a single dose administered at 12 months of age

End point title	Geometric Mean Ratios to baseline against a panel of genetically distinct meningococcal strains 30 days after a single dose administered at 12 months of age[21]

End point description:

Geometric Mean Ratios to baseline against a panel of genetically distinct meningococcal strains 30 days after a single dose administered at 12 months of age

End point type	Secondary

End point timeframe:

1 month after first vaccination

Notes:

[21] - 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	Routine	Routine+OMV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: Ratio				
geometric mean (confidence interval 95%)				
44/76-SL (1 month after first Vacc; N=22, 22)	1.51 (1.02 to 2.22)	3.21 (1.9 to 5.41)		
5/99 (1 month after first Vacc; N=21, 22)	73 (53 to 101)	8 (4.2 to 15)		
NZ98/254 (1 month after first Vacc; N=21, 22)	0.97 (0.9 to 1.04)	1.66 (1.12 to 2.45)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited AEs and unsolicited AEs were collected from Day 1 to Day 4; serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal were collected during the overall study period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	rMenB+OMV

Reporting group description:

Infants received 4 doses of rMenB vaccine with OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib- IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenCCRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Reporting group title	Routine+OMV

Reporting group description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine with OMV NZ at 12 months of age.

Reporting group title	rMenB

Reporting group description:

Infants received 4 doses of rMenB vaccine without OMV NZ at 2, 4, 6 and 12 months of age. Infants also received routine vaccines - 3 doses each of DTaPHib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and13 months), 2 doses of MenCCRM (at 3 and 5 months) and 1dose each of MenC-Hib (at 12 months) and MMR (at 13 months).

Reporting group title	Routine

Reporting group description:

Infants received routine vaccines - 3 doses each of DTaP-Hib-IPV (at 2, 3, and 4 months) and PC7 (at 2, 4 and 13 months), 2 doses of MenC-CRM (at 3 and 5 months) and 1 dose each of MenC-Hib (at 12 months) and MMR (at 13 months). Infants also received single dose of rMenB vaccine without OMV NZ at 12 months of age.

Serious adverse events	rMenB+OMV	Routine+OMV	rMenB
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 50 (18.00%)	2 / 24 (8.33%)	3 / 48 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 50 (0.00%)	0 / 24 (0.00%)	0 / 48 (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

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	0 / 48 (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
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	0 / 48 (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
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 50 (0.00%)	1 / 24 (4.17%)	0 / 48 (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
Musculoskeletal and connective tissue disorders			
Arthritis Reactive			
subjects affected / exposed	0 / 50 (0.00%)	0 / 24 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	0 / 48 (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

Croup Infectious			
subjects affected / exposed	0 / 50 (0.00%)	0 / 24 (0.00%)	0 / 48 (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
Gastroenteritis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 24 (0.00%)	0 / 48 (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
Gastroenteritis Viral			
subjects affected / exposed	0 / 50 (0.00%)	0 / 24 (0.00%)	0 / 48 (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
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 50 (4.00%)	0 / 24 (0.00%)	0 / 48 (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
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 24 (4.17%)	0 / 48 (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

Serious adverse events	Routine		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Hydrocele			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis Reactive			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Croup Infectious			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis Viral			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	0 / 25 (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	rMenB+OMV	Routine+OMV	rMenB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	24 / 24 (100.00%)	48 / 48 (100.00%)
Investigations			
Body Temperature Increased			
subjects affected / exposed	1 / 50 (2.00%)	1 / 24 (4.17%)	0 / 48 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	40 / 50 (80.00%)	20 / 24 (83.33%)	37 / 48 (77.08%)
occurrences (all)	127	48	97
General disorders and administration site conditions			
Crying			
subjects affected / exposed	24 / 50 (48.00%)	12 / 24 (50.00%)	26 / 48 (54.17%)
occurrences (all)	49	21	51
Injection Site Bruising			
subjects affected / exposed	4 / 50 (8.00%)	0 / 24 (0.00%)	4 / 48 (8.33%)
occurrences (all)	5	0	4
Injection Site Erythema			
subjects affected / exposed	49 / 50 (98.00%)	24 / 24 (100.00%)	47 / 48 (97.92%)
occurrences (all)	532	199	499
Injection Site Induration			
subjects affected / exposed	45 / 50 (90.00%)	24 / 24 (100.00%)	41 / 48 (85.42%)
occurrences (all)	275	130	218
Injection Site Pain			
subjects affected / exposed	37 / 50 (74.00%)	18 / 24 (75.00%)	36 / 48 (75.00%)
occurrences (all)	181	64	145
Vaccination Site Induration			
subjects affected / exposed	6 / 50 (12.00%)	3 / 24 (12.50%)	5 / 48 (10.42%)
occurrences (all)	8	3	9
Pyrexia			
subjects affected / exposed	15 / 50 (30.00%)	6 / 24 (25.00%)	11 / 48 (22.92%)
occurrences (all)	20	8	15
Vaccination Site Erythema			
subjects affected / exposed	4 / 50 (8.00%)	2 / 24 (8.33%)	3 / 48 (6.25%)
occurrences (all)	7	3	5
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	22 / 50 (44.00%)	12 / 24 (50.00%)	26 / 48 (54.17%)
occurrences (all)	32	29	53
Gastrooesophageal Reflux Disease			
subjects affected / exposed	2 / 50 (4.00%)	2 / 24 (8.33%)	1 / 48 (2.08%)
occurrences (all)	2	2	2
Teething			
subjects affected / exposed	15 / 50 (30.00%)	5 / 24 (20.83%)	11 / 48 (22.92%)
occurrences (all)	20	6	17
Vomiting			
subjects affected / exposed	16 / 50 (32.00%)	12 / 24 (50.00%)	22 / 48 (45.83%)
occurrences (all)	24	17	36
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 50 (20.00%)	5 / 24 (20.83%)	13 / 48 (27.08%)
occurrences (all)	13	7	15
Wheezing			
subjects affected / exposed	5 / 50 (10.00%)	1 / 24 (4.17%)	0 / 48 (0.00%)
occurrences (all)	7	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 50 (38.00%)	7 / 24 (29.17%)	20 / 48 (41.67%)
occurrences (all)	36	14	60
Eczema			
subjects affected / exposed	6 / 50 (12.00%)	4 / 24 (16.67%)	8 / 48 (16.67%)
occurrences (all)	6	6	9
Psychiatric disorders			
Irritability			
subjects affected / exposed	48 / 50 (96.00%)	24 / 24 (100.00%)	42 / 48 (87.50%)
occurrences (all)	222	81	170
Eating Disorder			
subjects affected / exposed	32 / 50 (64.00%)	12 / 24 (50.00%)	27 / 48 (56.25%)
occurrences (all)	72	20	52
Infections and infestations			
Bronchiolitis			

subjects affected / exposed	2 / 50 (4.00%)	0 / 24 (0.00%)	7 / 48 (14.58%)
occurrences (all)	3	0	9
Conjunctivitis			
subjects affected / exposed	5 / 50 (10.00%)	3 / 24 (12.50%)	8 / 48 (16.67%)
occurrences (all)	5	3	13
Gastroenteritis			
subjects affected / exposed	4 / 50 (8.00%)	0 / 24 (0.00%)	3 / 48 (6.25%)
occurrences (all)	4	0	3
Herpes Zoster			
subjects affected / exposed	1 / 50 (2.00%)	2 / 24 (8.33%)	0 / 48 (0.00%)
occurrences (all)	1	2	0
Gastroenteritis Viral			
subjects affected / exposed	2 / 50 (4.00%)	2 / 24 (8.33%)	3 / 48 (6.25%)
occurrences (all)	2	2	3
Otitis Media			
subjects affected / exposed	7 / 50 (14.00%)	1 / 24 (4.17%)	6 / 48 (12.50%)
occurrences (all)	7	1	6
Lower Respiratory Tract Infection			
subjects affected / exposed	12 / 50 (24.00%)	5 / 24 (20.83%)	5 / 48 (10.42%)
occurrences (all)	16	6	5
Upper Respiratory Tract Infection			
subjects affected / exposed	12 / 50 (24.00%)	2 / 24 (8.33%)	10 / 48 (20.83%)
occurrences (all)	13	2	10
Rhinitis			
subjects affected / exposed	19 / 50 (38.00%)	7 / 24 (29.17%)	19 / 48 (39.58%)
occurrences (all)	25	9	29
Varicella			
subjects affected / exposed	3 / 50 (6.00%)	1 / 24 (4.17%)	1 / 48 (2.08%)
occurrences (all)	3	1	1
Viral Infection			
subjects affected / exposed	2 / 50 (4.00%)	3 / 24 (12.50%)	1 / 48 (2.08%)
occurrences (all)	2	4	1
Viral Rash			
subjects affected / exposed	3 / 50 (6.00%)	1 / 24 (4.17%)	0 / 48 (0.00%)
occurrences (all)	3	1	0
Viral Upper Respiratory Tract			

Infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 24 (0.00%)	2 / 48 (4.17%)
occurrences (all)	2	0	2

Non-serious adverse events	Routine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Investigations			
Body Temperature Increased			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Nervous system disorders			
Somnolence			
subjects affected / exposed	22 / 25 (88.00%)		
occurrences (all)	52		
General disorders and administration site conditions			
Crying			
subjects affected / exposed	15 / 25 (60.00%)		
occurrences (all)	33		
Injection Site Bruising			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Injection Site Erythema			
subjects affected / exposed	25 / 25 (100.00%)		
occurrences (all)	211		
Injection Site Induration			
subjects affected / exposed	22 / 25 (88.00%)		
occurrences (all)	99		
Injection Site Pain			
subjects affected / exposed	13 / 25 (52.00%)		
occurrences (all)	50		
Vaccination Site Induration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	12		

Vaccination Site Erythema subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 13 / 25 (52.00%) 24 0 / 25 (0.00%) 0 3 / 25 (12.00%) 3 12 / 25 (48.00%) 23		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	 4 / 25 (16.00%) 4 1 / 25 (4.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all)	 10 / 25 (40.00%) 17 2 / 25 (8.00%) 2		
Psychiatric disorders Irritability subjects affected / exposed occurrences (all) Eating Disorder	 23 / 25 (92.00%) 84 		

subjects affected / exposed	15 / 25 (60.00%)		
occurrences (all)	35		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	3		
Conjunctivitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Herpes Zoster			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Gastroenteritis Viral			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Otitis Media			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	5		
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Varicella			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Viral Infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Viral Rash			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20954968