Clinical trial results:
A Phase IIIb, Open Label, Controlled, Multi-Center Study to Evaluate the Safety, Tolerability and Immunogenicity of Two Doses of Novartis Meningococcal Group B Vaccine when administered to Immunocompromised Patients from 2 to 17 years of age who are at Increased Risk of Meningococcal Disease because of Complement Deficiency or Asplenia compared to matched Healthy Controls.

Summary

EudraCT number	2013-002454-78
Trial protocol	IT ES PL
Global end of trial date	22 October 2015

Results information

Result version number	v1 (current)
This version publication date	19 March 2016
First version publication date	19 March 2016

Trial information

Trial identification

Sponsor protocol code	V72_62

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02141516
WHO universal trial number (UTN)	-
Other trial identifiers	Not applicable: Not applicable

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 and Diagnostics S.r.l., RegistryContactVaccinesUS@novartis.com
Scientific contact	Posting Director, Novartis Vaccines and Diagnostics S.r.l., 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2015
Global end of trial reached?	Yes
Global end of trial date	22 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Immunogenicity Objective
- To evaluate the immunogenicity of two doses of rMenB+OMV NZ in subjects with increased risk of meningococcal disease
because of complement deficiency or asplenia and in healthy age-matched subjects, at 1 month after the second vaccination.
Safety Objective
- To assess the safety and tolerability of two doses of rMenB+OMV NZ in subjects with increased risk of meningococcal disease
because of complement deficiency or asplenia and in healthy age-matched subjects.

Protection of trial subjects:

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations: including European Directive 2001/20/EC, Novartis codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Spain: 66
Country: Number of subjects enrolled	United Kingdom: 38
Country: Number of subjects enrolled	Italy: 33
Worldwide total number of subjects	239
EEA total number of subjects	194

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)	132
Adolescents (12-17 years)	107
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 4 centers in Italy, 3 centers in Poland, 3 centers in the Russian Federation, 4 centers in Spain and 4
centers in the United Kingdom.

Pre-assignment

Screening details:

All the enrolled subjects were included in the trial.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial is designed as an open-label study and all subjects will receive the same treatment.

Arms

Are arms mutually exclusive?	No
Arm title	CompDef

Arm description:

Subjects aged ≥ 2 to ≤ 17 years with complement deficiencies received 2 doses of rMenB+OMV NZ administered 2 months apart.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (group B)
Investigational medicinal product code	
Other name	rMenB+OMV NZ
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses of 0.5 mL each administered 2 months apart.

Arm title	Asplenia

Arm description:

Subjects aged ≥ 2 to ≤ 17 years with Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (group B)
Investigational medicinal product code	
Other name	rMenB+OMV NZ
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses of 0.5 mL each administered 2 months apart.

Arm title	CompDef+Asplenia

Arm description:

Subjects aged ≥ 2 to ≤ 17 years with either complement deficiencies or Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.

Arm type	Experimental

Investigational medicinal product name	Meningococcal (group B)
Investigational medicinal product code	
Other name	rMenB+OMV NZ
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses of 0.5 mL each administered 2 months apart.

Arm title	Healthy Subjects

Arm description:

Healthy subjects aged ≥ 2 to ≤ 17 years received 2 doses of rMenB+OMV NZ administered 2 months apart.

Arm type	Experimental
Investigational medicinal product name	Meningococcal (group B)
Investigational medicinal product code	
Other name	rMenB+OMV NZ
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Intramuscular use

Dosage and administration details:

Two doses of 0.5 mL each administered 2 months apart.

Number of subjects in period 1	CompDef	Asplenia	CompDef+Asplenia
Started	40	112	152
Completed	40	107	147
Not completed	0	5	5
Adverse event, non-fatal	-	1	1
Other	-	3	3
Lost to follow-up	-	1	1

Number of subjects in period 1	Healthy Subjects
Started	87
Completed	87
Not completed	0
Adverse event, non-fatal	-
Other	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	CompDef
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with complement deficiencies received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Asplenia
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	CompDef+Asplenia
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with either complement deficiencies or Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Healthy Subjects
Reporting group description:	
Healthy subjects aged ≥ 2 to ≤ 17 years received 2 doses of rMenB+OMV NZ administered 2 months apart.	

Reporting group values	CompDef	Asplenia	CompDef+Asplenia
Number of subjects	40	112	152
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	8.5	11.1	10.4
standard deviation	± 4.35	± 3.7	± 4.03
Gender categorical Units: Subjects			
Female	17	46	63
Male	23	66	89

Reporting group values	Healthy Subjects	Total	
Number of subjects	87	239	
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	10.2		
standard deviation	± 4.14	-	
Gender categorical Units: Subjects			
Female	44	107	
Male	43	132	

End points

End points reporting groups

Reporting group title	CompDef
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with complement deficiencies received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Asplenia
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	CompDef+Asplenia
Reporting group description:	
Subjects aged ≥ 2 to ≤ 17 years with either complement deficiencies or Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Healthy Subjects
Reporting group description:	
Healthy subjects aged ≥ 2 to ≤ 17 years received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Subject analysis set title	All Enrolled Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All screened subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's treatment status in the trial and received a subject ID.	
Subject analysis set title	Full Analysis Set (FAS), Immunogenicity Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the Enrolled Population who received a study vaccination and provided an evaluable serum sample at one month after the second dose of rMenB+OMV NZ whose assay result is available for at least one of the serogroup B indicator strains or M10713 strain or Enzyme-linked Immunosorbent Assay (ELISA).	
Subject analysis set title	Solicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set with any solicited adverse event data.	
Subject analysis set title	Unsolicited Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set with post-vaccination unsolicited adverse event records.	
Subject analysis set title	Overall Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects in the Exposed Set with any adverse event data.	

Primary: 1. Percentages of subjects with serum bactericidal activity using human complement (hSBA) titers ≥ 5 against N. meningitidis serogroup.

End point title	1. Percentages of subjects with serum bactericidal activity using human complement (hSBA) titers ≥ 5 against N. meningitidis serogroup.[1]
End point description:	
Immunogenicity was assessed in terms of percentage of subjects with hSBA titers ≥ 5 against N. meningitidis serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and M10713 strain following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61. The analysis was done on Full Analysis Set (FAS).	

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	106	144	85
Units: Percentages of Subjects				
number (confidence interval 95%)				
H44/76; Day 1 (N=39,104,143,84)	0 (0 to 9)	7 (2.7 to 13.4)	5 (2 to 9.8)	6 (2 to 13.3)
H44/76; Day 91 (N=39,104,143,85)	87 (72.6 to 95.7)	97 (91.8 to 99.4)	94 (89.3 to 97.6)	98 (91.8 to 99.71)
5/99; Day 1 (N=37,103,140,82)	0 (0 to 9.5)	12 (6.2 to 19.5)	9 (4.5 to 14.5)	6 (2 to 13.7)
5/99; Day 91 (N=38,106,144,83)	95 (82.3 to 99.4)	100 (96.6 to 100)	99 (95.1 to 99.83)	99 (93.5 to 99.97)
NZ98/254; Day 1 (N=36,105,141,83)	0 (0 to 9.7)	4 (1 to 9.5)	3 (0.8 to 7.1)	2 (0.29 to 8.4)
NZ98/254; Day 91 (N=38,106,144,84)	68 (51.3 to 82.5)	86 (77.7 to 91.9)	81 (73.9 to 87.3)	83 (73.6 to 90.6)
M10713; Day 1 (N=36,102,138,82)	56 (38.1 to 72.1)	79 (70.3 to 86.8)	73 (65 to 80.4)	78 (67.5 to 86.4)
M10713; Day 91 (N=37,103,140,83)	73 (55.9 to 86.2)	94 (87.8 to 97.8)	89 (82.1 to 93.3)	99 (93.5 to 99.97)

Statistical analyses

No statistical analyses for this end point

Primary: 2. Percentages of subjects with serum bactericidal activity hSBA titers ≥ 8 against N. meningitidis serogroup.

End point title	2. Percentages of subjects with serum bactericidal activity hSBA titers ≥ 8 against N. meningitidis serogroup.[2]

End point description:

Immunogenicity was assessed in terms of percentage of subjects with hSBA titers ≥ 8 against N. meningitidis serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and M10713 strain following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61. The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

Notes:

[2] - 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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	106	144	85
Units: Percentages of Subjects				
number (confidence interval 95%)				
H44/76; Day 1 (N=39,104,143,84)	0 (0 to 9)	2 (0.23 to 6.8)	1 (0.17 to 5)	2 (0.29 to 8.3)
H44/76; Day 91 (N=39,104,143,85)	87 (72.6 to 95.7)	95 (89.1 to 98.4)	93 (87.5 to 96.6)	98 (91.8 to 99.71)
5/99; Day 1 (N=37,103,140,82)	0 (0 to 9.5)	11 (5.5 to 18.3)	8 (4 to 13.6)	5 (1.3 to 12)
5/99; Day 91 (N=38,106,144,83)	92 (78.6 to 98.3)	100 (96.6 to 100)	98 (94 to 99.57)	99 (93.5 to 99.97)
NZ98/254; Day 1 (N=36,105,141,83)	0 (0 to 9.7)	4 (1 to 9.5)	3 (0.8 to 7.1)	0 (0 to 4.3)
NZ98/254; Day 91 (N=38,106,144,84)	63 (46 to 78.2)	79 (70.3 to 86.5)	75 (67.1 to 81.8)	73 (61.8 to 81.8)
M10713; Day 1 (N=36,102,138,82)	47 (30.4 to 64.5)	68 (57.7 to 76.6)	62 (53.7 to 70.4)	68 (57.1 to 78.1)
M10713; Day 91 (N=37,103,140,83)	70 (53 to 84.1)	94 (87.8 to 97.8)	88 (81.3 to 92.8)	98 (91.6 to 99.71)

Statistical analyses

No statistical analyses for this end point

Primary: 3. hSBA Geometric mean titers (GMTs) against N. meningitis serogroup B strains following a 2-dose vaccination schedule.

End point title	3. hSBA Geometric mean titers (GMTs) against N. meningitis serogroup B strains following a 2-dose vaccination schedule.[3]

End point description:

Immunogenicity was assessed in terms of GMTs against N. meningitidis serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and M10713 strain following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61. The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	106	144	85
Units: Titers				
geometric mean (confidence interval 95%)				
H44/76; Day 1 (N=39,104,143,84)	1.08 (0.87 to 1.33)	1.17 (1.03 to 1.32)	1.14 (1.03 to 1.26)	1.15 (1.03 to 1.28)
H44/76; Day 91 (N=39,104,143,85)	48 (29 to 79)	65 (48 to 88)	60 (46 to 77)	76 (61 to 94)
5/99; Day 1 (N=37,103,140,82)	0.87 (0.61 to 1.26)	1.43 (1.16 to 1.78)	1.26 (1.05 to 1.51)	1.24 (1.02 to 1.52)
5/99; Day 91 (N=38,106,144,83)	263 (166 to 415)	300 (230 to 392)	290 (231 to 362)	307 (250 to 376)

NZ98/254; Day 1 (N=36,105,141,83)	0.95 (0.78 to 1.16)	1.1 (0.98 to 1.24)	1.06 (0.96 to 1.17)	1.05 (0.98 to 1.12)
NZ98/254; Day 91 (N=38,106,144,84)	8.46 (4.85 to 15)	18 (13 to 24)	14 (11 to 19)	14 (10 to 18)
M10713; Day 1 (N=36,102,138,82)	8.57 (4.43 to 17)	15 (10 to 22)	13 (9.44 to 18)	16 (11 to 22)
M10713; Day 91 (N=37,103,140,83)	20 (11 to 34)	45 (33 to 62)	36 (28 to 47)	42 (34 to 52)

Statistical analyses

No statistical analyses for this end point

Primary: 4. Geometric mean ratios on Day 91 against N. meningitis serogroup B strains following a 2-dose vaccination schedule.

End point title	4. Geometric mean ratios on Day 91 against N. meningitis serogroup B strains following a 2-dose vaccination schedule.[4]

End point description:

Immunogenicity was assessed in terms of geometric mean ratios (GMRs) against N meningitidis serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and M10713 strain following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61. The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

Notes:

[4] - 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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	105	143	84
Units: Ratios				
geometric mean (confidence interval 95%)				
H44/76; Day 91/Day 1 (N=39,104,143,84)	44 (27 to 73)	56 (41 to 75)	52 (41 to 67)	66 (52 to 83)
5/99; Day 91/Day 1 (N=37,103,140,82)	299 (170 to 525)	207 (149 to 288)	228 (173 to 302)	245 (187 to 321)
NZ98/254; Day 91/Day 1 (N=36,105,141,83)	8.58 (4.9 to 15)	16 (12 to 22)	14 (10 to 18)	13 (10 to 17)
M10713; Day 91/Day 1 (N=36,102,138,82)	2.25 (1.37 to 3.71)	2.95 (2.21 to 3.95)	2.75 (2.15 to 3.51)	2.71 (2.02 to 3.65)

Statistical analyses

No statistical analyses for this end point

Primary: 5. Percentage of subjects with 4-fold increase in hSBA titers against N. meningitis serogroup B strains following a 2-dose vaccination.

End point title	5. Percentage of subjects with 4-fold increase in hSBA titers against N. meningitis serogroup B strains following a 2-dose

	vaccination.[5]

End point description:

Antibody responses were assessed in terms of percentage of subjects achieving 4-fold increase in hSBA titers against N. meningitidis serogroup B indicator strains (H44/76, 5/99, and NZ98/254) and M10713 strain on Day 91 over baseline (Day 1), following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61. The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 91 (one month after the second dose of the study vaccine).

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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	105	143	85
Units: Percentages of Subjects				
number (confidence interval 95%)				
H44/76 (N=39,104,143,84)	87 (72.6 to 95.7)	94 (87.9 to 97.9)	92 (86.7 to 96.1)	98 (91.7 to 99.71)
5/99 (N=37,103,140,82)	92 (78.1 to 98.3)	100 (96.5 to 100)	98 (93.9 to 99.56)	98 (91.5 to 99.7)
NZ98/254 (N=36,105,141,83)	61 (43.5 to 76.9)	80 (71.1 to 87.2)	75 (67.2 to 82.1)	73 (62.7 to 82.6)
M10713 (N=36,102,138,82)	25 (12.1 to 42.2)	33 (24.3 to 43.4)	31 (23.6 to 39.6)	33 (22.9 to 44.2)

Statistical analyses

No statistical analyses for this end point

Primary: 6. Geometric mean concentrations (GMCs) of antibodies against vaccine antigen 287-953 following a 2-dose vaccination schedule.

End point title	6. Geometric mean concentrations (GMCs) of antibodies against vaccine antigen 287-953 following a 2-dose vaccination schedule.[6]

End point description:

Immune responses were measured as ELISA GMCs of antibodies against vaccine antigen 287-953 following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61.The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

Notes:

[6] - 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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	106	146	84
Units: Concentrations				
geometric mean (confidence interval 95%)				
Antigen 287-953; Day 1 (N=39,106,145,84)	33 (25 to 43)	25 (21 to 29)	27 (23 to 31)	27 (23 to 31)
Antigen 287-953; Day 91 (N=40,106,146,84)	2039 (1436 to 2894)	3418 (2780 to 4202)	2973 (2492 to 3546)	2957 (2450 to 3570)

Statistical analyses

No statistical analyses for this end point

Primary: 7. ELISA GMRs on Day 91 against vaccine antigen 287-953 following a 2-dose vaccination schedule.

End point title	7. ELISA GMRs on Day 91 against vaccine antigen 287-953 following a 2-dose vaccination schedule.[7]

End point description:

Immune responses were measured as ELISA GMRs against vaccine antigen 287-953 following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day 61.The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 1 and Day 91 (one month after the second dose of the study vaccine).

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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	106	145	84
Units: Ratios				
geometric mean (confidence interval 95%)				
Antigen 287-953 Day 91/Day 1 (N=39,106,145,84)	62 (40 to 97)	138 (107 to 178)	112 (90 to 139)	111 (88 to 140)

Statistical analyses

No statistical analyses for this end point

Primary: 8. Percentage of subjects with 4-fold increase in ELISA concentrations against N. meningitis serogroup B strains following a 2-dose vaccination schedule.

End point title	8. Percentage of subjects with 4-fold increase in ELISA concentrations against N. meningitis serogroup B strains following a 2-dose vaccination schedule.[8]

End point description:

Antibody responses were assessed in terms of percentage of subjects achieving 4-fold increase in ELISA concentrations against
vaccine antigen 287-953 on Day 91 over baseline (Day 1), following 2 doses of rMenB+OMV NZ, administered on Day 1 and Day
61. The analysis was done on Full Analysis Set (FAS).

End point type	Primary

End point timeframe:

Day 91 (one month after the second dose of the study vaccine).

Notes:

[8] - 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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	106	146	84
Units: Percentages of Subjects				
number (confidence interval 95%)				
Antigen 287-953 (N=39,106,145,84)	97 (86.5 to 99.94)	98 (93.4 to 99.77)	98 (94.1 to 99.57)	98 (91.7 to 99.71)

Statistical analyses

No statistical analyses for this end point

Primary: 9. Number Of Subjects With Solicited Local or Systemic Adverse Events.

End point title	9. Number Of Subjects With Solicited Local or Systemic Adverse Events.[9]

End point description:

Safety was assessed as the number of subjects who reported solicited local or systemic adverse events (AEs) following administration of rMenB+OMV NZ vaccine. The analysis was done on the Solicited Safety Set.

End point type	Primary

End point timeframe:

Day 1 through Day 7 after any 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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	100	128	74[10]
Units: Subjects				
Any Local (< 6 years; N=12,9,21,13)	12	6	18	12
Injection Site Tendern. (< 6 years; N=12,9,21,13)	12	6	18	12
Injection Site Erythema (< 6 years; N=12,9,21,13)	7	4	11	6
Injection Site Indur. (< 6 years; N=12,9,21,13)	5	4	9	5

Any Local (≥ 6 years)	26	98	124	74
Injection Site Pain (≥ 6 years)	25	97	122	71
Injection Site Erythema (≥ 6 years)	7	19	26	27
Injection Site Swelling (≥ 6 years)	8	24	32	24
Injection Site Indur. (≥ 6 years)	11	27	38	19
Any Systemic (< 6 years)	11	6	17	12
Change in Eating Habits (< 6 years; N=12,9,21,13)	5	1	6	8
Persistent Crying (< 6 years; N=12,9,21,13)	2	2	4	6
Irritability (< 6 years; N=12,9,21,13)	6	2	8	9
Vomiting (< 6 years; N=12,9,21,13)	2	0	2	0
Diarrhea (< 6 years; N=12,9,21,13)	5	3	8	3
Fever (≥38°C) (< 6 years; N=12,9,21,13)	3	1	4	4
Rash (< 6 years; N=12,9,21,13)	3	0	3	0
Any Others (< 6 years; N=12,9,21,13)	12	8	20	13
Prev. Pain/Fever (< 6 years; N=12,9,21,13)	5	1	6	4
Use of Analg./Antipyr. (< 6 years; N=12,9,21,13)	5	3	8	11
Any Systemic (≥ 6 years)	21	75	96	60
Nausea (≥ 6 years)	7	28	35	15
Fatigue (≥ 6 years)	11	55	66	46
Myalgia (≥ 6 years)	8	31	39	27
Arthralgia (≥ 6 years)	7	25	32	18
Headache (≥ 6 years)	11	47	58	35
Fever (≥38°C) (≥ 6 years)	6	6	12	5
Rash (≥ 6 years)	7	9	16	6
Prev. Pain/Fever (≥6 years)	5	9	14	15
Use of Analg./Antipyr. (≥ 6 years)	14	39	53	38
Any Others (≥ 6 years)	27	98	125	74
Sleepiness (< 6 years; N=12,9,21,13)	7	3	10	5
Injection Site Swelling (< 6 years; N=12,9,21,13)	6	4	10	6

Notes:

[10] - Only for Myalgia (>= 6 years) N = 28,100,128,73.

Statistical analyses

No statistical analyses for this end point

Primary: 10. Number Of Subjects With Unsolicited Adverse Events.

End point title	10. Number Of Subjects With Unsolicited Adverse Events.[11]

End point description:

Safety was assessed as the number of subjects who reported unsolicited AEs collected from Day 1 through Day 7 after any vaccination; serious adverse events (SAEs), AEs leading to withdrawal and medically attended AEs were collected throughout the study period. The analysis was done on the Unsolicited Safety Set.

End point type	Primary

End point timeframe:

Day 1 through Day 7 after any vaccination; throughout the study period.

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: No statistical analysis was associated to this endpoint. Analyses were run descriptively.

End point values	CompDef	Asplenia	CompDef+Asplenia	Healthy Subjects
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	110	150	87
Units: Subjects				
Any AE	17	38	55	34
At least possibly related unsolicited AEs	9	19	28	18
Any SAEs	1	5	6	0
At least Possibly Related SAEs	0	0	0	0
AEs leading to death	0	0	0	0
AEs Leading to Withdrawal	0	1	1	0
MEdically Attended AEs	13	26	39	18

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the study period.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	CompDef
Reporting group description: Subjects aged ≥2 to ≤17 years with complement deficiencies received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Asplenia
Reporting group description: Subjects aged ≥2 to ≤17 years with Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	CompDef + Asplenia
Reporting group description: Subjects aged ≥2 to ≤17 years with either complement deficiencies or Asplenia received 2 doses of rMenB+OMV NZ administered 2 months apart.	
Reporting group title	Healthy Subjects
Reporting group description: Healthy subjects aged ≥2 to ≤17 years received 2 doses of rMenB+OMV NZ administered 2 months apart.	

Serious adverse events	CompDef	Asplenia	CompDef + Asplenia
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	5 / 110 (4.55%)	6 / 150 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Intracardiac thrombus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 40 (2.50%)	0 / 110 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 110 (0.91%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Healthy Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 87 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Intracardiac thrombus			

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis salmonella			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	0 / 87 (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	CompDef	Asplenia	CompDef + Asplenia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)	106 / 110 (96.36%)	145 / 150 (96.67%)
Nervous system disorders			
Headache			

subjects affected / exposed	11 / 40 (27.50%)	48 / 110 (43.64%)	59 / 150 (39.33%)
occurrences (all)	15	70	85
Somnolence			
subjects affected / exposed	7 / 40 (17.50%)	3 / 110 (2.73%)	10 / 150 (6.67%)
occurrences (all)	11	4	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 40 (27.50%)	55 / 110 (50.00%)	66 / 150 (44.00%)
occurrences (all)	19	89	108
Injection site erythema			
subjects affected / exposed	15 / 40 (37.50%)	23 / 110 (20.91%)	38 / 150 (25.33%)
occurrences (all)	18	34	52
Injection site induration			
subjects affected / exposed	17 / 40 (42.50%)	32 / 110 (29.09%)	49 / 150 (32.67%)
occurrences (all)	30	48	78
Injection site pain			
subjects affected / exposed	37 / 40 (92.50%)	103 / 110 (93.64%)	140 / 150 (93.33%)
occurrences (all)	72	196	268
Injection site swelling			
subjects affected / exposed	14 / 40 (35.00%)	28 / 110 (25.45%)	42 / 150 (28.00%)
occurrences (all)	23	45	68
Pyrexia			
subjects affected / exposed	10 / 40 (25.00%)	7 / 110 (6.36%)	17 / 150 (11.33%)
occurrences (all)	11	9	20
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 40 (17.50%)	28 / 110 (25.45%)	35 / 150 (23.33%)
occurrences (all)	12	42	54
Diarrhoea			
subjects affected / exposed	5 / 40 (12.50%)	4 / 110 (3.64%)	9 / 150 (6.00%)
occurrences (all)	5	6	11
Vomiting			
subjects affected / exposed	3 / 40 (7.50%)	0 / 110 (0.00%)	3 / 150 (2.00%)
occurrences (all)	3	0	3
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	10 / 40 (25.00%)	9 / 110 (8.18%)	19 / 150 (12.67%)
occurrences (all)	12	10	22
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	5 / 40 (12.50%)	1 / 110 (0.91%)	6 / 150 (4.00%)
occurrences (all)	8	1	9
Irritability			
subjects affected / exposed	7 / 40 (17.50%)	2 / 110 (1.82%)	9 / 150 (6.00%)
occurrences (all)	14	5	19
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 40 (17.50%)	25 / 110 (22.73%)	32 / 150 (21.33%)
occurrences (all)	11	38	49
Myalgia			
subjects affected / exposed	8 / 40 (20.00%)	31 / 110 (28.18%)	39 / 150 (26.00%)
occurrences (all)	13	44	57

Non-serious adverse events	Healthy Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 87 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	35 / 87 (40.23%)		
occurrences (all)	59		
Somnolence			
subjects affected / exposed	5 / 87 (5.75%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	46 / 87 (52.87%)		
occurrences (all)	67		
Injection site erythema			
subjects affected / exposed	34 / 87 (39.08%)		
occurrences (all)	49		
Injection site induration			

subjects affected / exposed	26 / 87 (29.89%)		
occurrences (all)	36		
Injection site pain			
subjects affected / exposed	83 / 87 (95.40%)		
occurrences (all)	171		
Injection site swelling			
subjects affected / exposed	32 / 87 (36.78%)		
occurrences (all)	46		
Pyrexia			
subjects affected / exposed	10 / 87 (11.49%)		
occurrences (all)	11		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 87 (17.24%)		
occurrences (all)	21		
Diarrhoea			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 87 (6.90%)		
occurrences (all)	8		
Psychiatric disorders			
Eating disorder			
subjects affected / exposed	8 / 87 (9.20%)		
occurrences (all)	13		
Irritability			
subjects affected / exposed	9 / 87 (10.34%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 87 (20.69%)		
occurrences (all)	24		

Myalgia subjects affected / exposed occurrences (all)	27 / 87 (31.03%) 34		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2014	The first version of the protocol was issued on June 20, 2013 and subsequently 3 amendments were issued. A total of 2 protocol amendments were issued before FSFV and 1 was issued after FSFV: - Amendment 1 was issued on July 22, 2013 and occurred before any clinical trial application and aims to correct minor inconsistencies, was classified as non-substantial; - Amendment 2 was issued on October 16, 2013 and occurred before any clinical trial application and after the review of clinical study protocol by the Committee for Medicinal Products for Human Use (CHMP). It included feedback and recommendation from the CHMP, was classified as substantial; - Amendment 3 was issued on July 30, 2014 it occurred after FSFV and it was classified as substantial: Amendment no 3 of protocol was issued to allow for additional study participants. Although the additional participants allowed for greater precision in the estimation of the study parameters, the sample size for this study was driven by feasibility and regulatory considerations, and not by formal statistical assumptions. Thus, no changes in the analysis and interpretation of results were foreseen. The protocol amendment permitted the screening of subjects who have already been booked in the UK, as per recommendation of a local EC, as well as the participation of subjects in Russian centers which had received Health Authority approval after the preamendment enrollment target for patients at increased risk of meningococcal disease had been reached. According to clinical study protocol amendment no 3, approximately 240 subjects (ie, up to 160 patients at increased risk of meningococcal disease and approximately 80 matched healthy subjects) meeting all eligibility criteria were to be enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported