



Clinical trial results:

A Phase 3b, Open Label, Controlled, Multi-Center, Extension Study to Assess the Persistence of Bactericidal Activity at 4 to 7.5 Years After Two Dose Primary Series of GlaxoSmithKline Biologicals Meningococcal B Recombinant Vaccine and the Response to a Third Dose in Adolescents and Young Adult Subjects who Previously Participated in Parent Studies V72_41 and V72P10, Compared to Naïve Healthy Controls **Summary**

| | |
|--------------------------|-------------------|
| EudraCT number | 2017-000093-11 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 23 September 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 |
| This version publication date | 30 November 2017 |
| First version publication date | 14 October 2017 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 205218 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02446743 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330 |
| Public contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 June 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 September 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 September 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To assess and compare the safety and tolerability of a single dose (booster) of rMenB+OMV NZ administered to follow-on subjects approximately 4 to 7.5 years after a 2 dose primary series, with that of two doses of rMenB+OMV NZ administered to naïve subjects according to a 0, 1-month schedule.
- To assess serum bactericidal activity at approximately 4 to 7.5 years following a 2 dose primary series (persistence) compared to serum bactericidal activity at baseline in vaccination-naïve subjects.

Protection of trial subjects:

The subjects were observed closely for at least 30 minutes following the administration of vaccine(s), with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 November 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Australia: 63 |
| Country: Number of subjects enrolled | Canada: 187 |
| Country: Number of subjects enrolled | Chile: 281 |
| Worldwide total number of subjects | 531 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 122 |
| Adults (18-64 years) | 409 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 4 sites in Australia, 6 sites in Canada and 2 sites in Chile.

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

Period 1

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

Blinding implementation details:

The study was an open- label study. Therefore, no blinding procedures were utilized.

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 3B |

Arm description:

Subjects who received a third dose booster of rMenB+OMV NZ at 4 to 7.5 years after the last dose received during studies V72P10 (NCT00661713) or V72_41(NCT0142384), and had blood collected at baseline and at 3, 7 and 30 days after the third dose booster.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | GlaxoSmithKline Meningococcal group B multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose (0.5 mL) vaccine administered by intramuscular (IM) injection in the deltoid area of the nondominant arm

| | |
|------------------|-------------|
| Arm title | Group B_0_1 |
|------------------|-------------|

Arm description:

Subjects who received two doses of rMenB+OMV NZ at a 0 and 1 month schedule and had blood collected at baseline, 30 days after the first dose and 3 or 7, and 30 days after the second dose.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GlaxoSmithKline Meningococcal group B multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose (0.5 mL) vaccine administered by intramuscular (IM) injection in the deltoid area of the nondominant arm

| Number of subjects in period 1 | Group 3B | Group B_0_1 |
|---------------------------------------|----------|-------------|
| Started | 276 | 255 |
| Completed | 271 | 250 |
| Not completed | 5 | 5 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 1 | 1 |
| Unspecified | 2 | 3 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Group 3B |
|-----------------------|----------|

Reporting group description:

Subjects who received a third dose booster of rMenB+OMV NZ at 4 to 7.5 years after the last dose received during studies V72P10 (NCT00661713) or V72_41(NCT0142384), and had blood collected at baseline and at 3, 7 and 30 days after the third dose booster.

| | |
|-----------------------|-------------|
| Reporting group title | Group B_0_1 |
|-----------------------|-------------|

Reporting group description:

Subjects who received two doses of rMenB+OMV NZ at a 0 and 1 month schedule and had blood collected at baseline, 30 days after the first dose and 3 or 7, and 30 days after the second dose.

| Reporting group values | Group 3B | Group B_0_1 | Total |
|--|----------|-------------|-------|
| Number of subjects | 276 | 255 | 531 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age<37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 65 | 57 | 122 |
| Adults (18-64 years) | 211 | 198 | 409 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 19.5 | 20.0 | |
| standard deviation | ± 2.42 | ± 2.69 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 133 | 128 | 261 |
| Male | 143 | 127 | 270 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Race/Ethnicity American Indian or Alaska Native | 11 | 1 | 12 |
| Race/Ethnicity Asian | 22 | 18 | 40 |
| Race/Ethnicity Black or African American | 3 | 2 | 5 |
| Race/Ethnicity NativeHawaiian/pacific Islander | 3 | 8 | 11 |
| Race/Ethnicity White | 98 | 74 | 172 |
| Race/Ethnicity Other | 139 | 152 | 291 |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Group 3B |
| Reporting group description: Subjects who received a third dose booster of rMenB+OMV NZ at 4 to 7.5 years after the last dose received during studies V72P10 (NCT00661713) or V72_41(NCT0142384), and had blood collected at baseline and at 3, 7 and 30 days after the third dose booster. | |
| Reporting group title | Group B_0_1 |
| Reporting group description: Subjects who received two doses of rMenB+OMV NZ at a 0 and 1 month schedule and had blood collected at baseline, 30 days after the first dose and 3 or 7, and 30 days after the second dose. | |

Primary: Percentage of subjects with human serum bactericidal activity (hSBA) $\geq 1:5$

| | |
|---|---|
| End point title | Percentage of subjects with human serum bactericidal activity (hSBA) $\geq 1:5$ |
| End point description: Bactericidal activity was measured against each of the N. meningitidis group B indicator strains H44/76, 5/99, NZ98/254 and M10713. | |
| End point type | Primary |
| End point timeframe: Group 3B: Day 1 (prior to booster dose); Group B_0_1: Day 1 (prior to first dose). | |

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 33 (27.9 to 39.4) | 9 (5.5 to 12.8) | | |
| 5/99 | 84 (78.7 to 88.2) | 15 (10.4 to 19.8) | | |
| NZ98/254 | 18 (13.3 to 22.6) | 8 (5.2 to 12.4) | | |
| M10713 | 74 (68.9 to 79.5) | 70 (64.2 to 75.7) | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis group B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.2 |
| upper limit | 31.4 |

Notes:

[1] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis group B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 62.3 |
| upper limit | 75 |

Notes:

[2] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis group B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.6 |
| upper limit | 15.1 |

Notes:

[3] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis group B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 11.9 |

Notes:

[4] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

Primary: Percentage of subjects with hSBA \geq 1:8

| | |
|--|---|
| End point title | Percentage of subjects with hSBA \geq 1:8 |
| End point description: Bactericidal activity was measured against each of the N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713 | |
| End point type | Primary |
| End point timeframe: Group 3B: Day 1 (prior to booster dose); Group B_0_1: Day 1 (prior to first dose). | |

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 28 (23.1 to 34.1) | 6 (3.3 to 9.5) | | |
| 5/99 | 81 (75.3 to 85.4) | 13 (9.0 to 17.9) | | |
| NZ98/254 | 14 (10.4 to 19.0) | 6 (3.1 to 9.1) | | |
| M10713 | 68 (62.0 to 73.4) | 63 (56.9 to 69.1) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis group B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.5 |
| upper limit | 28.6 |

Notes:

[5] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|--|-------------------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis group B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 60.8 |
| upper limit | 73.7 |

Notes:

[6] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 3 |
|--|------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis group B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.7 |
| upper limit | 14 |

Notes:

[7] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis group B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 12.8 |

Notes:

[8] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

Primary: Percentage of subjects with hSBA \geq 1:16

| | |
|-----------------|--|
| End point title | Percentage of subjects with hSBA \geq 1:16 |
|-----------------|--|

End point description:

Bactericidal activity was measured against each of the N. meningitidis group B Indicator strains H44/76,5/99,NZ98/254 and M10713

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Group 3B: Day 1 (prior to booster dose); Group B_0_1: Day 1 (prior to first dose).

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 20 (15.1 to 24.8) | 4 (2.2 to 7.6) | | |
| 5/99 | 75 (69.0 to 80.0) | 8 (5.2 to 12.6) | | |
| NZ98/254 | 11 (7.8 to 15.7) | 2 (0.9 to 5.1) | | |
| M10713 | 57 (51.2 to 63.2) | 56 (49.4 to 61.9) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------------|
| Statistical analysis description: | |
| The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.1 |
| upper limit | 20.9 |

Notes:

[9] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|---|-------------------------------------|
| Statistical analysis description: | |
| The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[10] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 66 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 59.6 |
| upper limit | 72.4 |

Notes:

[10] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.9 |
| upper limit | 13.6 |

Notes:

[11] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[12] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.8 |
| upper limit | 10 |

Notes:

[12] - Vaccine comparison at Persistence at 4/7.5 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

Primary: hSBA Geometric Mean Titers (GMTs) after the last dose of rMenB+OMV NZ vaccination in the parent study.

| | |
|-----------------|--|
| End point title | hSBA Geometric Mean Titers (GMTs) after the last dose of |
|-----------------|--|

End point description:

Bactericidal activity was measured against each of the N. meningitidis group B indicator strains H44/76, 5/99, NZ98/254 and M10713.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Group 3B: 1 month after the last rMenB+OMV NZ vaccination in parent study and Day 1(prior to booster dose); Group B_0_1: Day 1(prior to first dose)

| End point values | Group 3B | Group B_0_1 | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76(1 month post last vacc in parent study) | 124 (108 to 143) | 0 (0 to 0) | | |
| H44/76(Day 1) | 3.05 (2.61 to 3.56) | 1.20 (1.02 to 1.42) | | |
| 5/99(1 month post last vacc in parent study) | 270 (234 to 311) | 0 (0 to 0) | | |
| 5/99 (Day 1) | 26 (21 to 31) | 1.57 (1.26 to 1.95) | | |
| NZ98/254(1 month post last vacc in parent study) | 22 (19 to 27) | 0 (0 to 0) | | |
| NZ98/254(Day 1) | 1.66 (1.46 to 1.89) | 1.11 (0.97 to 1.27) | | |
| M10713(1 month post last vacc in parent study) | 19 (16 to 24) | 0 (0 to 0) | | |
| M10713(Day 1) | 16 (13 to 20) | 12 (9.86 to 16) | | |

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Adjusted geometric mean titers for H44/76 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[13] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratio of GMTs |
| Point estimate | 2.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.07 |
| upper limit | 3.12 |

Notes:

[13] - Vaccine Comparison at Persistence at 4 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|--|-----------------------------|
| Statistical analysis description: Adjusted geometric mean titers for 5/99 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[14] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratio of GMTs |
| Point estimate | 16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12 |
| upper limit | 21 |

Notes:

[14] - Vaccine Comparison at Persistence at 4 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 3 |
|---|-----------------------------|
| Statistical analysis description: Adjusted geometric mean titers for NZ98/254 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[15] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratio of GMTs |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.26 |
| upper limit | 1.78 |

Notes:

[15] - Vaccine Comparison at Persistence at 4 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 4 |
|---|------------------------|
| Statistical analysis description: Adjusted geometric mean titers for M10713 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 530 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[16] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratio of GMTs |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.68 |

Notes:

[16] - Vaccine Comparison at Persistence at 4 years/Baseline in V72_75 (Group 3B vs. Group B_0_1)

Primary: Geometric Mean Ratios (GMRs) of GMTs after the last dose of rMenB+OMV NZ Vaccination in the Parent Study.

| | |
|-----------------|---|
| End point title | Geometric Mean Ratios (GMRs) of GMTs after the last dose of rMenB+OMV NZ Vaccination in the Parent Study. ^{[17][18]} |
|-----------------|---|

End point description:

The GMRs of GMTs at Day 1 versus one month after the last dose of rMenB+OMV NZ vaccination in the parent study were calculated. Bactericidal activity was measured against each of the N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Group 3B: 1 month after the last vaccination in parent study and Day1 (prior to booster dose)

Notes:

[17] - 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: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

[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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group 3B | | | |
|--|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 275 | | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 | 0.025 (0.020 to 0.030) | | | |
| 5/99 | 0.098 (0.079 to 0.12) | | | |
| NZ98/254 | 0.073 (0.059 to 0.089) | | | |
| M10713 | 0.81 (0.65 to 1.01) | | | |

Statistical analyses

Primary: Number of subjects with solicited local and systemic AEs.

| | |
|-----------------|---|
| End point title | Number of subjects with solicited local and systemic AEs. ^[19] |
|-----------------|---|

End point description:

Solicited adverse events are signs and symptoms derived from organized data collection systems, such as Subject Diaries or interview. The percentage and frequencies of subjects reporting solicited local and systemic AEs were tabulated. Threshold for any Erythema, Swelling and Induration: ≥ 25 mm

Note: Vaccination 2 was performed only on group B_0_1 subjects.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

7 days (including the day of vaccination) after each vaccination

Notes:

[19] - 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: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

| End point values | Group 3B | Group B_0_1 | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 266 | 254 | | |
| Units: Subjects | | | | |
| Any | 263 | 251 | | |
| Any Local (vaccination 1) | 258 | 247 | | |
| Injection site pain (vaccination 1) | 258 | 247 | | |
| Erythema (vaccination 1) | 54 | 18 | | |
| Swelling (vaccination 1) | 60 | 34 | | |
| Induration (vaccination 1) | 54 | 26 | | |
| Any systemic (vaccination 1) | 203 | 163 | | |
| Fever ($\geq 38.0^{\circ}\text{C}$) (vaccination 1) | 16 | 4 | | |
| High fever ($\geq 39.5^{\circ}\text{C}$) (vaccination 1) | 0 | 0 | | |
| Nausea (vaccination 1) | 56 | 30 | | |
| Fatigue (vaccination 1) | 155 | 110 | | |
| Myalgia (vaccination 1) | 120 | 71 | | |
| Arthralgia (vaccination 1) | 84 | 47 | | |
| Headache (vaccination 1) | 146 | 94 | | |
| Any Local (vaccination 2) | 0 | 226 | | |
| Injection site pain (vaccination 2) | 0 | 226 | | |
| Erythema (vaccination 2) | 0 | 21 | | |
| Swelling (vaccination 2) | 0 | 32 | | |
| Induration (vaccination 2) | 0 | 31 | | |
| Any systemic (vaccination 2) | 0 | 140 | | |
| Fever ($\geq 38.0^{\circ}\text{C}$) (vaccination 2) | 0 | 5 | | |
| High fever ($\geq 39.5^{\circ}\text{C}$) (vaccination 2) | 0 | 0 | | |
| Nausea (vaccination 2) | 0 | 33 | | |
| Fatigue (vaccination 2) | 0 | 92 | | |
| Myalgia (vaccination 2) | 0 | 64 | | |
| Arthralgia (vaccination 2) | 0 | 36 | | |
| Headache (vaccination 2) | 0 | 84 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with any unsolicited adverse events (AEs).

| | |
|-----------------|--|
| End point title | Number of subjects with any unsolicited adverse events |
|-----------------|--|

End point description:

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary and that was spontaneously communicated by a subject and/or parent(s)/legal guardian(s) who has signed the informed consent. Note : Vaccination 2 was performed only on group B_0_1 subjects.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

30 days (including the day of vaccination) after each vaccination.

Notes:

[20] - 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: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

| End point values | Group 3B | Group B_0_1 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Subjects | | | | |
| Any | 87 | 131 | | |
| Any unsolicited AEs (vaccination 1) | 87 | 96 | | |
| Any unsolicited AEs (vaccination 2) | 0 | 73 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with any SAEs, AEs leading to withdrawal and medically attended AEs.

| | |
|-----------------|---|
| End point title | Number of subjects with any SAEs, AEs leading to withdrawal and medically attended AEs. ^[21] |
|-----------------|---|

End point description:

A serious adverse event is any untoward medical occurrence that at any dose results in death or is life threatening or requires prolonged hospitalization, leads to Persistent or significant disability/incapacity.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Group 3B: from Day 1 to Day 31 (30 days after the vaccination) and Group B_0_1: from Day 1 to Day 61 (30 days after the second dose)

Notes:

[21] - 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: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

| End point values | Group 3B | Group B_0_1 | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 | 255 | | |
| Units: Subjects | | | | |
| Any SAEs | 0 | 1 | | |
| Any Medically Attended AEs | 17 | 34 | | |
| Any AEs leading to premature withdrawal | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with hSBA $\geq 1:5$ after booster dose/first vaccination of rMenB+OMV NZ.

| | |
|-----------------|---|
| End point title | Percentage of subjects with hSBA $\geq 1:5$ after booster dose/first vaccination of rMenB+OMV NZ. |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: 1 month after booster dose, Group B_0_1 : 30 days after first vaccination.

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 99 (96.8 to 99.77) | 79 (73.5 to 83.9) | | |
| 5/99 | 100 (98.4 to 100.0) | 84 (78.9 to 88.6) | | |
| NZ98/254 | 93 (88.9 to 95.6) | 52 (45.4 to 58.1) | | |
| M10713 | 99 (96.8 to 99.77) | 87 (82.1 to 90.8) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen

| | |
|-------------------|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
|-------------------|------------------------|

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[22] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 20 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15 |
| upper limit | 25.4 |

Notes:

[22] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[23] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.7 |
| upper limit | 21 |

Notes:

[23] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[24] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 41 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 33.9 |
| upper limit | 47.8 |

Notes:

[24] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|--|-------------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[25] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8 |
| upper limit | 16.8 |

Notes:

[25] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

Secondary: Percentage of subjects with hSBA $\geq 1:8$ after booster dose/first vaccination of rMenB+OMV NZ

| | |
|--|--|
| End point title | Percentage of subjects with hSBA $\geq 1:8$ after booster dose/first vaccination of rMenB+OMV NZ |
| End point description: Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. | |
| End point type | Secondary |

End point timeframe:

Group 3B : 1 month after booster dose, Group B_0_1 : 30 days after first vaccination.

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 99 (96.8 to 99.77) | 72 (65.6 to 77.0) | | |
| 5/99 | 100 (98.4 to 100.0) | 81 (75.6 to 86.0) | | |
| NZ98/254 | 87 (82.8 to 91.2) | 45 (38.4 to 51.0) | | |
| M10713 | 98 (95.7 to 99.4) | 85 (79.9 to 89.1) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[26] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.9 |
| upper limit | 33.3 |

Notes:

[26] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|---|-------------------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[27] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.3 |
| upper limit | 24.3 |

Notes:

[27] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 3 |
|--|------------------------|
| Statistical analysis description: The group difference in percentages of subjects with response against N. meningitidis serogroup B | |

indicator strain NZ98/254 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[28] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 35.2 |
| upper limit | 49.9 |

Notes:

[28] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference were calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[29] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.8 |
| upper limit | 18.3 |

Notes:

[29] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

Secondary: Percentage of subjects with hSBA $\geq 1:16$ after booster dose/first vaccination of rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Percentage of subjects with hSBA $\geq 1:16$ after booster dose/first vaccination of rMenB+OMV NZ |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: 1 month after booster dose, Group B_0_1 : 30 days after first vaccination.

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 99 (96.2 to 99.59) | 58 (52.2 to 64.6) | | |
| 5/99 | 100 (98.4 to 100.0) | 73 (66.9 to 78.6) | | |
| NZ98/254 | 79 (73.6 to 83.8) | 36 (29.9 to 42.1) | | |
| M10713 | 95 (91.8 to 97.4) | 77 (70.9 to 81.7) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------------|
| Statistical analysis description: | |
| The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[30] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 40 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 33.9 |
| upper limit | 46.3 |

Notes:

[30] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|---|-------------------------------------|
| Statistical analysis description: | |
| The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[31] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 27 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 21.6 |
| upper limit | 33 |

Notes:

[31] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[32] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 35.1 |
| upper limit | 50.6 |

Notes:

[32] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[33] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.9 |
| upper limit | 24.6 |

Notes:

[33] - Vaccine comparison at 1 month after booster /1st dose in V72_75 (Group 3B vs. Group B_0_1)

Secondary: hSBA Geometric Mean Titers prior to booster/first dose of vaccination & post booster/first dose of vaccination.

| | |
|-----------------|---|
| End point title | hSBA Geometric Mean Titers prior to booster/first dose of |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four *N. meningitidis* group B indicator strains H44/76, 5/99, NZ98/254 and M10713

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B subjects: Day 1(pre-booster dose) and 1 month post-booster dose. Group B_0_1: Day 1 (pre-first dose) and 30 days post-first dose.

| End point values | Group 3B | Group B_0_1 | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76- pre booster/ pre first dose | 3.10 (2.65 to 3.62) | 1.19 (1.01 to 1.41) | | |
| H44/76-1 month post booster/first dose | 188 (155 to 228) | 16 (13 to 20) | | |
| 5/99- pre booster/ pre first dose | 24 (19 to 30) | 1.51 (1.21 to 1.88) | | |
| 5/99-1 month post booster/first dose | 2089 (1690 to 2582) | 31 (25 to 38) | | |
| NZ98/254-pre booster/ pre first dose | 1.64 (1.44 to 1.86) | 1.11 (0.97 to 1.28) | | |
| NZ98/254-1 month post booster/first dose | 32 (26 to 39) | 5.39 (4.33 to 6.72) | | |
| M10713-pre booster/ pre first dose | 16 (13 to 20) | 12 (9.62 to 15) | | |
| M10713-1 month post booster/first dose | 78 (66 to 92) | 30 (25 to 36) | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Pre booster/Pre first dose-Adjusted geometric mean titers for H44/76 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country.

| | |
|---|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[34] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratios |
| Point estimate | 2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.11 |
| upper limit | 3.2 |

Notes:

[34] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 2 |
|--|------------------------|
| Statistical analysis description: Post booster/Post first dose-Adjusted geometric mean titers for H44/76 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[35] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratios |
| Point estimate | 11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.85 |
| upper limit | 15 |

Notes:

[35] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 3 |
|--|------------------------|
| Statistical analysis description: Pre booster/Pre first dose-Adjusted geometric mean titers for 5/99 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[36] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratios |
| Point estimate | 16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12 |
| upper limit | 21 |

Notes:

[36] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B_0_1)

| Statistical analysis title | Statistical analysis 4 |
|--|------------------------|
| Statistical analysis description: Post booster/Post first dose-Adjusted geometric mean titers for 5/99 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group 3B v Group B_0_1 |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[37] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratios |
| Point estimate | 68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 51 |
| upper limit | 90 |

Notes:

[37] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B _0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

Pre booster/Pre first dose-Adjusted geometric mean titers for NZ98/254 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country

| | |
|---|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[38] |
| Method | ANOVA |
| Parameter estimate | Vaccine group ratios |
| Point estimate | 1.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.24 |
| upper limit | 1.75 |

Notes:

[38] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B _0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

post booster dose/ first dose-Adjusted geometric mean titers for NZ98/254 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country.

| | |
|---|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[39] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratios |
| Point estimate | 5.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.49 |
| upper limit | 7.76 |

Notes:

[39] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B _0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

Pre booster/Pre first dose-Adjusted geometric mean titers for M10713 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country

| | |
|---|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[40] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratios |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 1.75 |

Notes:

[40] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B _0_1)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

Post booster/Post first dose-Adjusted geometric mean titers for M10713 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country

| | |
|---|------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 521 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[41] |
| Method | ANOVA |
| Parameter estimate | vaccine group ratios |
| Point estimate | 2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.08 |
| upper limit | 3.25 |

Notes:

[41] - Vaccine comparison Pre-booster or pre-1st dose in V72_75 (Group 3B vs. Group B _0_1)

Secondary: Geometric mean ratio (GMRs) of GMTs after booster dose/first rMenB+OMV NZ vaccination.

| | |
|--|--|
| End point title | Geometric mean ratio (GMRs) of GMTs after booster dose/first rMenB+OMV NZ vaccination. |
| End point description: Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76, 5/99, NZ98/254 and M10713 by calculating the GMRs of GMTs one month post-vaccination of a booster dose versus pre-booster dose (follow-on subjects) or first dose of rMenB+OMV NZ versus pre-first dose (naïve subjects) to each N. meningitidis group B indicator strain. | |
| End point type | Secondary |
| End point timeframe: At Day 31 (30 days post booster dose/first dose of vaccination) versus Day 1 (prior to booster dose/first dose of vaccination). | |

| End point values | Group 3B | Group B_0_1 | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 | 61 (50 to 74) | 14 (11 to 17) | | |
| 5/99 | 87 (67 to 112) | 20 (16 to 26) | | |
| NZ98/254 | 19 (16 to 24) | 4.92 (3.97 to 6.10) | | |
| M10713 | 4.85 (4.10 to 5.72) | 2.44 (2.04 to 2.91) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of subjects with at least 4-fold increase in hSBA titers pre vaccination compared to one month post-booster/first rMenB+OMV NZ vaccination

| | |
|--|--|
| End point title | Percentages of subjects with at least 4-fold increase in hSBA titers pre vaccination compared to one month post-booster/first rMenB+OMV NZ vaccination |
| End point description: The percentage of subjects with 4-fold rise at one month post-vaccination with a booster dose (follow-on subjects) /first dose (naïve subjects) of rMenB+OMV NZ with respect to day 1 (follow-on subjects) / pre-first dose of rMenB+OMV NZ (naïve subjects) | |
| End point type | Secondary |
| End point timeframe: Group 3B: 1 month after booster dose; Group B_0_1: 1 month after first vaccination | |

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 268 | 253 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 96 (93.2 to 98.2) | 70 (63.5 to 75.2) | | |
| 5/99 | 98 (94.6 to 99.2) | 76 (69.9 to 81.4) | | |
| NZ98/254 | 80 (75.0 to 85.0) | 43 (36.3 to 49.0) | | |
| M10713 | 49 (42.6 to 54.9) | 26 (20.5 to 31.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with hSBA $\geq 1:5$ after booster dose/second vaccination of rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Percentage of subjects with hSBA $\geq 1:5$ after booster dose/second vaccination of rMenB+OMV NZ |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. On day 1, subjects in the Group B_0_1 were to be randomized into 2 different blood draw schedules according to a 1:1 ratio : 2 blood samples at different time points: Group B_0_1_1: blood draws at 3 and 30 days after the second dose. Group B_0_1_2: blood draws at 7 and 30 days after the second dose.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: 3, 7 and 30 days after third dose booster; Group B_0_1: At 3 (group B_0_1_1 only), 7 (sub-group B_0_1_2 only) and 30 days post-second dose."

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 3 days post vaccination | 36 (30.3 to 42.8) | 80 (71.1 to 87.2) | | |
| H44/76 7 days post vaccination | 98 (95.2 to 99.3) | 99 (94.4 to 99.97) | | |
| H44/76 1 month post vaccination | 99 (96.4 to 99.74) | 99 (96.5 to 99.88) | | |
| 5/99- 3 days post-vaccination | 78 (71.7 to 84.1) | 83 (72.9 to 89.9) | | |
| 5/99- 7 days post-vaccination | 100 (98.0 to 100.0) | 99 (93.8 to 99.97) | | |
| 5/99- 1 month post-vaccination | 100 (98.0 to 100.0) | 99 (95.9 to 99.86) | | |

| | | | | |
|------------------------------------|--------------------|-------------------|--|--|
| NZ98/254- 3 days post-vaccination | 18 (12.9 to 23.1) | 44 (34.1 to 53.8) | | |
| NZ98/254- 7 days post-vaccination | 74 (67.7 to 79.3) | 79 (69.1 to 86.2) | | |
| NZ98/254- 1 month post-vaccination | 93 (88.6 to 95.7) | 76 (69.9 to 82.0) | | |
| M10713- 3 days post-vaccination | 78 (72.2 to 83.1) | 82 (73.2 to 88.7) | | |
| M10713- 7 days post-vaccination | 98 (94.7 to 99.1) | 96 (89.9 to 98.9) | | |
| M10713- 1 month post-vaccination | 99 (97.0 to 99.90) | 93 (88.7 to 96.2) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[42] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -52.7 |
| upper limit | -33.1 |

Notes:

[42] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[43] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 3.6 |

Notes:

[43] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 3 |
|---|-------------------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[44] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7 |
| upper limit | 2.4 |

Notes:

[44] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 4 |
|--|-------------------------------------|
| Statistical analysis description: 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[45] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.6 |
| upper limit | 6.6 |

Notes:

[45] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 5 |
|--|------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[46] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 6.2 |

Notes:

[46] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[47] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 4.1 |

Notes:

[47] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[48] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.9 |
| upper limit | -15.7 |

Notes:

[48] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 8 |
|--|-------------------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[49] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.1 |
| upper limit | 5.8 |

Notes:

[49] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 9 |
|---|-------------------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[50] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.8 |
| upper limit | 23.3 |

Notes:

[50] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 10 |
|--|-------------------------|
| Statistical analysis description: 3 days post vaccination-The group difference in percentages of subjects with response N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group 3B v Group B_0_1 |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[51] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.4 |
| upper limit | 5.8 |

Notes:

[51] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[52] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 7.7 |

Notes:

[52] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group 3B v Group B_0_1 |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[53] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.8 |
| upper limit | 10.5 |

Notes:

[53] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

Secondary: Percentage of subjects with hSBA $\geq 1:8$ after booster dose/second vaccination of rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Percentage of subjects with hSBA $\geq 1:8$ after booster dose/second vaccination of rMenB+OMV NZ |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four *N. meningitidis* group B indicator strains H44/76,5/99,NZ98/254 and M10713. On day 1, subjects in the Group B_0_1 were to be randomized into 2 different blood draw schedules according to a 1:1 ratio : 2 blood samples at different time points: Group B_0_1_1: blood draws at 3 and 30 days after the second dose. Group B_0_1_2: blood draws at 7 and 30 days after the second dose.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: 3, 7 and 30 days after third dose booster; Group B_0_1: At 3 (group B_0_1_1 only), 7 (sub-group B_0_1_2 only) and 30 days post-second dose.

| End point values | Group 3B | Group B_0_1 | | |
|------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 3 days post vaccination | 30 (24.5 to 36.4) | 75 (65.9 to 83.1) | | |
| H44/76 7 days post vaccination | 96 (93.1 to 98.3) | 97 (91.3 to 99.4) | | |
| H44/76 1 month post vaccination | 99 (96.4 to 99.74) | 98 (95.0 to 99.5) | | |
| 5/99- 3 days post-vaccination | 76 (69.4 to 82.2) | 83 (72.9 to 89.9) | | |
| 5/99- 7 days post-vaccination | 100 (98.0 to 100.0) | 99 (93.8 to 99.97) | | |
| 5/99- 1 month post-vaccination | 100 (98.0 to 100.0) | 99 (95.9 to 99.86) | | |
| NZ98/254- 3 days post-vaccination | 16 (11.4 to 21.2) | 42 (32.3 to 51.9) | | |
| NZ98/254- 7 days post-vaccination | 67 (60.1 to 72.6) | 69 (59.3 to 78.3) | | |
| NZ98/254- 1 month post-vaccination | 88 (82.6 to 91.5) | 67 (60.1 to 73.4) | | |
| M10713- 3 days post-vaccination | 70 (63.5 to 75.4) | 73 (63.8 to 81.5) | | |
| M10713- 7 days post-vaccination | 95 (92.0 to 97.7) | 94 (87.1 to 97.7) | | |
| M10713- 1 month post-vaccination | 98 (95.8 to 99.55) | 90 (85.2 to 93.9) | | |

Statistical analyses

| | |
|--|-------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[54] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -54.4 |
| upper limit | -34.3 |

Notes:

[54] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[55] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | 5.2 |

Notes:

[55] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|--|------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: | |
| 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[56] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 3.9 |

Notes:

[56] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[57] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -15.9 |
| upper limit | 4.6 |

Notes:

[57] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[58] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 6.2 |

Notes:

[58] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 6 |
|---|-------------------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[59] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 4.1 |

Notes:

[59] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 7 |
|--|-------------------------------------|
| Statistical analysis description: 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[60] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -36.6 |
| upper limit | -15.7 |

Notes:

[60] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 8 |
|--|------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[61] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.3 |
| upper limit | 8.5 |

Notes:

[61] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[62] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.8 |
| upper limit | 28.3 |

Notes:

[62] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[63] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.4 |
| upper limit | 7.1 |

Notes:

[63] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 11 |
|--|-------------------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[64] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 8.5 |

Notes:

[64] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| Statistical analysis title | Statistical analysis 12 |
|---|-------------------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[65] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.2 |
| upper limit | 13.2 |

Notes:

[65] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

Secondary: Percentage of subjects with hSBA \geq 1:16 after booster dose/second vaccination of rMenB+OMV NZ

| | |
|-----------------|--|
| End point title | Percentage of subjects with hSBA \geq 1:16 after booster dose/second vaccination of rMenB+OMV NZ |
|-----------------|--|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. On day 1, subjects in the Group B_0_1 were to be randomized into 2 different blood draw schedules according to a 1:1 ratio : 2 blood samples at different time points: Group B_0_1_1: blood draws at 3 and 30 days after the second dose. Group B_0_1_2: blood draws at 7

and 30 days after the second dose.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Group 3B: 3, 7 and 30 days after third dose booster; Group B_0_1: At 3 (group B_0_1_1 only), 7 (sub-group B_0_1_2 only) and 30 days post-second dose | |

| End point values | Group 3B | Group B_0_1 | | |
|------------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 3 days post vaccination | 21 (15.7 to 26.3) | 50 (40.5 to 60.4) | | |
| H44/76 7 days post vaccination | 95 (91.0 to 97.1) | 92 (84.5 to 96.4) | | |
| H44/76 1 month post vaccination | 99 (96.4 to 99.74) | 91 (86.3 to 94.7) | | |
| 5/99- 3 days post-vaccination | 70 (63.1 to 76.8) | 76 (65.1 to 84.2) | | |
| 5/99- 7 days post-vaccination | 100 (98.0 to 100.0) | 99 (93.8 to 99.97) | | |
| 5/99- 1 month post-vaccination | 100 (98.0 to 100.0) | 98 (95.0 to 99.64) | | |
| NZ98/254- 3 days post-vaccination | 9 (6.0 to 13.9) | 30 (21.0 to 39.2) | | |
| NZ98/254- 7 days post-vaccination | 51 (44.5 to 57.7) | 47 (36.8 to 57.3) | | |
| NZ98/254- 1 month post-vaccination | 81 (75.0 to 85.6) | 49 (41.7 to 55.9) | | |
| M10713- 3 days post-vaccination | 59 (52.0 to 64.8) | 64 (53.9 to 73.0) | | |
| M10713- 7 days post-vaccination | 88 (83.2 to 91.8) | 88 (79.6 to 93.5) | | |
| M10713- 1 month post-vaccination | 95 (91.5 to 97.4) | 84 (78.5 to 89.0) | | |

Statistical analyses

| | |
|--|-------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[66] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -30 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.4 |
| upper limit | -19 |

Notes:

[66] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[67] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.6 |
| upper limit | 10.3 |

Notes:

[67] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[68] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.9 |
| upper limit | 12.5 |

Notes:

[68] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N.

meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[69] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16 |
| upper limit | 6.5 |

Notes:

[69] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[70] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 6.2 |

Notes:

[70] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[71] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 2 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.33 |
| upper limit | 5 |

Notes:

[71] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[72] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -20 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30 |
| upper limit | -11.1 |

Notes:

[72] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[73] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 15.7 |

Notes:

[73] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N.

meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[74] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 23.2 |
| upper limit | 40.2 |

Notes:

[74] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[75] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16 |
| upper limit | 6 |

Notes:

[75] - Vaccine comparison at Day 4 Group 3B vs Day 34 Group B_0_1 (3 days after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[76] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 0 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.8 |
| upper limit | 8.9 |

Notes:

[76] - Vaccine comparison at Day 8 Group 3B vs Day 38 Group B_0_1 (7 days after booster or 2nd dose)

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 12 |
|-----------------------------------|-------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[77] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.3 |
| upper limit | 16.9 |

Notes:

[77] - Vaccine comparison at Day 31 Group 3B vs Day 61 Group B_0_1 (1 month after booster or 2nd dose)

Secondary: hSBA Geometric Mean Titers prior to booster/second dose of vaccination & post booster/second dose of vaccination.

| | |
|-----------------|---|
| End point title | hSBA Geometric Mean Titers prior to booster/second dose of vaccination & post booster/second dose of vaccination. |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. On day 1, subjects in the Group B_0_1 were to be randomized into 2 different blood draw schedules according to a 1:1 ratio : 2 blood samples at different time points: Group B_0_1_1: blood draws at 3 and 30 days after the second dose. Group B_0_1_2: blood draws at 7 and 30 days after the second dose.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: Day 1 (pre-booster dose) and 3, 7 and 30 days after third dose booster; Group B_0_1: Pre 2nd dose and at 3 (group B_0_1_1 only), 7 (group B_0_1_2 only) and 30 days post second dose.

| | | | | |
|--|-----------------|-----------------|--|--|
| End point values | Group 3B | Group B_0_1 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |

| | | | | |
|------------------------------|---------------------|---------------------|--|--|
| H44/76 - pre-vaccination | 2.99 (2.41 to 3.70) | 17 (14 to 22) | | |
| H44/76 - 3 days post-vacc | 3.20 (2.60 to 3.94) | 17 (13 to 23) | | |
| H44/76 - 7 days post-vacc | 115 (98 to 136) | 57 (44 to 73) | | |
| H44/76 - 1 month post-vacc. | 196 (170 to 228) | 56 (48 to 66) | | |
| 5/99- pre-vaccination | 24 (18 to 32) | 31 (23 to 41) | | |
| 5/99- 3 days post-vacc | 24 (18 to 31) | 27 (19 to 41) | | |
| 5/99- 7 days post-vacc | 1787 (1477 to 2162) | 337 (257 to 442) | | |
| 5/99- 1 month post-vacc. | 2026 (1714 to 2395) | 248 (208 to 295) | | |
| NZ98/254- pre-vaccination | 1.57 (1.29 to 1.92) | 5.11 (4.10 to 6.38) | | |
| NZ98/254- 3 days post-vacc | 1.62 (1.35 to 1.96) | 4.45 (3.38 to 5.84) | | |
| NZ98/254- 7 days post-vacc | 12 (10 to 15) | 12 (8.46 to 16) | | |
| NZ98/254- 1 month post-vacc. | 35 (29 to 42) | 14 (11 to 17) | | |
| M10713- pre-vaccination | 15 (12 to 19) | 32 (25 to 41) | | |
| M10713- 3 days post-vacc | 16 (13 to 21) | 23 (17 to 33) | | |
| M10713- 7 days post-vacc | 54 (46 to 62) | 45 (36 to 57) | | |
| M10713- 1 month post-vacc. | 78 (67 to 92) | 41 (35 to 49) | | |

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Adjusted geometric mean titers for H44/76 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[78] |
| Method | ANOVA |
| Parameter estimate | vaccine group difference |
| Point estimate | 3.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.85 |
| upper limit | 4.29 |
| Notes: | |
| [78] - Vaccine Comparison Day 31 Group 3B vs Day 61 Group B_0_1(1 month after booster or 2nd dose) | |
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Adjusted geometric mean titers for 5/99 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[79] |
| Method | ANOVA |
| Parameter estimate | vaccine group difference |
| Point estimate | 8.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.51 |
| upper limit | 10 |

Notes:

[79] - Vaccine Comparison Day 31 Group 3B vs Day 61 Group B_0_1(1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Adjusted geometric mean titers for NZ98/254 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country

| | |
|---|--------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[80] |
| Method | ANOVA |
| Parameter estimate | vaccine group difference |
| Point estimate | 2.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.98 |
| upper limit | 3.36 |

Notes:

[80] - Vaccine Comparison Day 31 Group 3B vs Day 61 Group B_0_1(1 month after booster or 2nd dose)

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 4 |
|-----------------------------------|------------------------|

Statistical analysis description:

Adjusted geometric mean titers for M10713 indicator strain were obtained by exponentiating (base 10) the least square means and the lower and upper limits of the 95% confidence intervals of the log-transformed titers obtained from an ANOVA estimation adjusting for vaccine group and country

| | |
|---|--------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[81] |
| Method | ANOVA |
| Parameter estimate | vaccine group difference |
| Point estimate | 1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.52 |
| upper limit | 2.36 |

Notes:

[81] - Vaccine Comparison Day 31 Group 3B vs Day 61 Group B_0_1(1 month after booster or 2nd dose)

Secondary: Geometric Mean Ratios (GMRs) of GMTs after booster/second vaccination versus before booster/second vaccination.

| | |
|-----------------|---|
| End point title | Geometric Mean Ratios (GMRs) of GMTs after booster/second vaccination versus before booster/second vaccination. |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713 by calculating the GMRs of GMTs post-vaccination with a booster dose (Group 3B) versus pre-booster dose or second dose (Group B_0_1) of vaccination versus pre-second dose.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: Day 1 and 30 days after third dose booster; Group B_0_1: 30 days post-first dose and at 30 days post-second dose

| End point values | Group 3B | Group B_0_1 | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 | 66 (55 to 79) | 3.27 (2.66 to 4.03) | | |
| 5/99 | 85 (65 to 111) | 8.10 (6.12 to 11) | | |
| NZ98/25 | 22 (19 to 27) | 2.63 (2.15 to 3.21) | | |
| M10713 | 5.07 (4.33 to 5.94) | 1.27 (1.07 to 1.52) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with at Least Four-fold Increase in hSBA Titers Pre-booster/Second dose vaccination- compared to 3, 7 and 30 Days Post-booster/Second Vaccination

| | |
|-----------------|--|
| End point title | Percentages of Subjects with at Least Four-fold Increase in hSBA Titers Pre-booster/Second dose vaccination- compared to 3, 7 and 30 Days Post- booster/Second Vaccination |
|-----------------|--|

End point description:

The percentage of subjects with 4-fold rise at three, seven, thirty days post-vaccination with a booster dose (follow-on subjects) /second dose (naïve subjects) of rMenB+OMV NZ with respect to day 1 (follow-on subjects) / pre-second dose of rMenB+OMV NZ (naïve subjects). Percentage of subjects with four-fold rise in hSBA titers relative to baseline were defined as: • for a pre-vaccination titer < 4, a post-vaccination titer of at least 16; • for a pre-vaccination titer ≥ 4 but <LLOQ, a post vaccination titer of at least fourfold the LLOQ; • for a pre-vaccination titer ≥LLOQ, a post vaccination titer of at least fourfold the pre-vaccination titer

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Group 3B: at 3, 7 and 30 days after third dose booster; Group B_0_1: at 3 (group B_0_1_1 only), 7 (group B_0_1_2 only) and 30 days post second dose

| End point values | Group 3B | Group B_0_1 | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 242 | 203 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 3 days post vaccination | 2 (0.7 to 4.8) | 4 (1.0 to 9.5) | | |
| H44/76 - 7 days post-vacc | 88 (82.8 to 91.5) | 35 (25.4 to 45.0) | | |
| H44/76 - 1 month post-vacc. | 96 (93.1 to 98.3) | 38 (31.7 to 45.5) | | |
| 5/99- 3 days post-vacc | 5 (2.0 to 8.8) | 6 (2.0 to 13.5) | | |
| 5/99- 7 days post-vacc | 97 (92.7 to 98.7) | 59 (48.2 to 69.8) | | |
| 5/99- 1 month post-vacc. | 97 (93.5 to 99.1) | 64 (56.8 to 71.7) | | |
| NZ98/254- 3 days post-vacc | 2 (0.7 to 5.0) | 2 (0.23 to 6.8) | | |
| NZ98/254- 7 days post-vacc | 55 (48.3 to 61.5) | 19 (11.4 to 27.7) | | |
| NZ98/254- 1 month post-vacc. | 81 (75.3 to 85.8) | 27 (21.3 to 34.1) | | |
| M10713- 3 days post-vacc | 3 (0.9 to 5.4) | 0 (0.0 to 3.5) | | |
| M10713- 7 days post-vacc | 34 (27.8 to 40.1) | 6 (2.3 to 13.0) | | |
| M10713- 1 month post-vacc. | 49 (42.3 to 55.3) | 9 (5.8 to 14.3) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------------------|
| Statistical analysis description: | |
| 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[82] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 1.8 |

Notes:

[82] - 3 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 2 |
|---|-------------------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[83] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 42.1 |
| upper limit | 62.5 |

Notes:

[83] - 7 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 3 |
|--|-------------------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain H44/76 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[84] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 50.5 |
| upper limit | 64.7 |

Notes:

[84] - 1 Month Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 4 |
|---|------------------------|
| Statistical analysis description: 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[85] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.1 |
| upper limit | 4 |

Notes:

[85] - 3 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 5 |
|-----------------------------------|------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[86] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 27 |
| upper limit | 48.1 |

Notes:

[86] - 7 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 6 |
|-----------------------------------|------------------------|

Statistical analysis description:

1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain 5/99 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[87] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 33 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 25.2 |
| upper limit | 40.4 |

Notes:

[87] - 1 Month Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 7 |
|--|-------------------------------------|
| Statistical analysis description: 3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[88] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | 3.4 |

Notes:

[88] - 3 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 8 |
|---|-------------------------------------|
| Statistical analysis description: 7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[89] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 25.6 |
| upper limit | 45.7 |

Notes:

[89] - 7 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| Statistical analysis title | Statistical analysis 9 |
|--|------------------------|
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain NZ98/254 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen. | |
| Comparison groups | Group B_0_1 v Group 3B |

| | |
|---|-------------------------------------|
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[90] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 45.2 |
| upper limit | 61.1 |

Notes:

[90] - 1 Month Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 10 |
|-----------------------------------|-------------------------|

Statistical analysis description:

3 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[91] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 5.4 |

Notes:

[91] - 3 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| | |
|-----------------------------------|-------------------------|
| Statistical analysis title | Statistical analysis 11 |
|-----------------------------------|-------------------------|

Statistical analysis description:

7 days post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen.

| | |
|---|-------------------------------------|
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[92] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 19.1 |
| upper limit | 34.9 |

Notes:

[92] - 7 Days Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical analysis 12 |
| Statistical analysis description: 1 month post vaccination-The group difference in percentages of subjects with response against N. meningitidis serogroup B indicator strain M10713 and the associated confidence interval for the difference was calculated using the method of Miettinen and Nurminen | |
| Comparison groups | Group B_0_1 v Group 3B |
| Number of subjects included in analysis | 445 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[93] |
| Method | Miettinen and Nurminen score method |
| Parameter estimate | vaccine group difference |
| Point estimate | 39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 31.6 |
| upper limit | 46.6 |

Notes:

[93] - 1 Month Post Booster/Second Vaccination. Four-fold Increase (Group 3B vs. Group B_0_1) Difference

Secondary: Percentage of subjects with hSBA $\geq 1:5$ after second vaccination of rMenB+OMV NZ

| | |
|---|--|
| End point title | Percentage of subjects with hSBA $\geq 1:5$ after second vaccination of rMenB+OMV NZ ^[94] |
| End point description: Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. Only subjects receiving a second vaccination (group B_0_1) were assessed for this outcome measure. | |
| End point type | Secondary |
| End point timeframe: At Day 61 (30 days post second dose of vaccination.) | |

Notes:

[94] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| | | | | |
|----------------------------------|--------------------|--|--|--|
| End point values | Group B_0_1 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 99 (96.7 to 99.89) | | | |
| 5/99 | 98 (95.6 to 99.68) | | | |
| NZ98/254 | 77 (70.5 to 82.2) | | | |

| | | | | |
|--------|-------------------|--|--|--|
| M10713 | 93 (88.7 to 96.0) | | | |
|--------|-------------------|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with hSBA $\geq 1:8$ after second vaccination of rMenB+OMV NZ.

| | |
|-----------------|---|
| End point title | Percentage of subjects with hSBA $\geq 1:8$ after second vaccination of rMenB+OMV NZ. ^[95] |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76,5/99,NZ98/254 and M10713. Only subjects receiving a second vaccination (group B_0_1) were assessed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 61 (30 days post second vaccination)

Notes:

[95] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group B_0_1 | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 98 (95.3 to 99.5) | | | |
| 5/99 | 98 (95.6 to 99.68) | | | |
| NZ98/254 | 67 (60.3 to 73.2) | | | |
| M10713 | 90 (85.4 to 93.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with hSBA $\geq 1:16$ after second vaccination of rMenB+OMV NZ.

| | |
|-----------------|--|
| End point title | Percentage of subjects with hSBA $\geq 1:16$ after second vaccination of rMenB+OMV NZ. ^[96] |
|-----------------|--|

End point description:

Bactericidal activity was measured against each of the four *N. meningitidis* group B indicator strains H44/76,5/99,NZ98/254 and M10713. Only subjects receiving a second vaccination (group B_0_1) were assessed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 61 (30 days post second vaccination)

Notes:

[96] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group B_0_1 | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 91 (86.0 to 94.2) | | | |
| 5/99 | 98 (94.8 to 99.4) | | | |
| NZ98/254 | 48 (41.5 to 55.3) | | | |
| M10713 | 84 (78.5 to 88.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: hSBA Geometric Mean Titers (GMTs) after second vaccination of rMenB+OMV NZ.

| | |
|-----------------|---|
| End point title | hSBA Geometric Mean Titers (GMTs) after second vaccination of rMenB+OMV NZ. ^[97] |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four *N. meningitidis* group B indicator strains H44/76,5/99,NZ98/254 and M10713. Only subjects receiving a second vaccination (group B_0_1) were assessed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 1 & Day 61 (30 days post second dose of vaccination)

Notes:

[97] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group B_0_1 | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 Day 1 | 1.32 (1.18 to 1.47) | | | |
| H44/76 1 month post 2nd vaccination | 61 (53 to 70) | | | |
| 5/99 Day 1 | 1.63 (1.35 to 1.96) | | | |
| 5/99 1 month post 2nd vaccination | 257 (217 to 305) | | | |
| NZ98/254 Day 1 | 1.28 (1.15 to 1.42) | | | |
| NZ98/254 1 month post 2nd vaccination | 14 (11 to 17) | | | |
| M10713 Day 1 | 14 (11 to 18) | | | |
| M10713 1 month post 2nd vaccination | 46 (38 to 55) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean ratio (GMRs) of GMTs one month post second vaccination versus pre vaccination at Day 1

| | |
|-----------------|---|
| End point title | Geometric mean ratio (GMRs) of GMTs one month post second vaccination versus pre vaccination at Day 1 ^[98] |
|-----------------|---|

End point description:

Bactericidal activity was measured against each of the four N. meningitidis group B indicator strains H44/76, 5/99, NZ98/254 and M10713. Only subjects receiving a second vaccination (group B_0_1) were assessed for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 1 & Day 61 (30 days post 2nd vaccination)

Notes:

[98] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group B_0_1 | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Ratio | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 | 46 (39 to 54) | | | |
| 5/99 | 156 (117 to 209) | | | |
| NZ98/254 | 11 (8.88 to 14) | | | |
| M10713 | 3.23 (2.76 to 3.77) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with at Least Four-fold Increase in hSBA Titers at pre-First Vaccination compared to One Month Post-Second Vaccination

| | |
|-----------------|--|
| End point title | Percentages of Subjects with at Least Four-fold Increase in hSBA Titers at pre-First Vaccination compared to One Month Post-Second Vaccination ^[99] |
|-----------------|--|

End point description:

The percentage of subjects with 4-fold rise at one month post-vaccination with a second dose (naïve subjects) of rMenB+OMV NZ with respect to day 1, to each and any one, two, three or all 4 indicator strains. Percentage of subjects with four-fold rise in hSBA titers relative to baseline were defined as: • for a pre-vaccination titer < 4, a post-vaccination titer of at least 16; • for a pre-vaccination titer ≥ 4 but <LLOQ, a post vaccination titer of at least fourfold the LLOQ; • for a pre-vaccination titer ≥LLOQ, a post vaccination titer of at least fourfold the pre-vaccination titer. Only subjects receiving the second dose of vaccination(group B_0_1) were considered for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Day 61 (30 days post second dose of vaccination)

Notes:

[99] - 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: The results in this study were tabulated by age group and study period. Hence for each related endpoint, they are presented for only the respective groups in the baseline period, while the results for multiple endpoints account for all baseline groups.

| End point values | Group B_0_1 | | | |
|----------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 215 | | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 | 95 (91.6 to 97.7) | | | |
| 5/99 | 97 (92.9 to 98.8) | | | |
| NZ98/254 | 67 (59.9 to 73) | | | |
| M10713 | 35 (28.2 to 41.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs were collected until 7 days after vaccinations. Unsolicited AEs were collected 30 days after vaccination at day 31 (all subjects) and at day 61 (group B_0_1 subjects only).

Adverse event reporting additional description:

Serious Adverse Events (SAEs) were collected until study termination (1 month for group 3B subjects/ 2 months for group B_0_1 subjects)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Group B_0_1 |
|-----------------------|-------------|

Reporting group description:

Subjects who received two doses of rMenB+OMV NZ at a 0 and 1 month schedule and had blood collected at baseline, 30 days after the first dose and 3 or 7, and 30 days after the second dose.

| | |
|-----------------------|----------|
| Reporting group title | Group 3B |
|-----------------------|----------|

Reporting group description:

Subjects who received a third dose booster of rMenB+OMV NZ at 4 to 7.5 years after the last dose received during studies V72P10 (NCT00661713) or V72_41(NCT0142384), and had blood collected at baseline and at 3, 7 and 30 days after the third dose booster.

| Serious adverse events | Group B_0_1 | Group 3B | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 255 (0.39%) | 0 / 275 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 255 (0.39%) | 0 / 275 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Group B_0_1 | Group 3B | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 253 / 255 (99.22%) | 266 / 275 (96.73%) | |
| Nervous system disorders | | | |

| | | | |
|---|----------------------------|----------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 126 / 255 (49.41%) 442 | 150 / 275 (54.55%) 361 | |
| General disorders and administration site conditions | | | |
| Injection site pain subjects affected / exposed occurrences (all) | 251 / 255 (98.43%) 2029 | 259 / 275 (94.18%) 1088 | |
| Injection site erythema subjects affected / exposed occurrences (all) | 135 / 255 (52.94%) 724 | 162 / 275 (58.91%) 575 | |
| Fatigue subjects affected / exposed occurrences (all) | 141 / 255 (55.29%) 489 | 156 / 275 (56.73%) 394 | |
| Injection site induration subjects affected / exposed occurrences (all) | 136 / 255 (53.33%) 834 | 135 / 275 (49.09%) 548 | |
| Injection site swelling subjects affected / exposed occurrences (all) | 111 / 255 (43.53%) 675 | 123 / 275 (44.73%) 475 | |
| Pyrexia subjects affected / exposed occurrences (all) | 9 / 255 (3.53%) 16 | 17 / 275 (6.18%) 22 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 53 / 255 (20.78%) 128 | 56 / 275 (20.36%) 113 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia subjects affected / exposed occurrences (all) | 100 / 255 (39.22%) 313 | 121 / 275 (44.00%) 291 | |
| Arthralgia subjects affected / exposed occurrences (all) | 63 / 255 (24.71%) 212 | 85 / 275 (30.91%) 203 | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 23 / 255 (9.02%) | 13 / 275 (4.73%) | |
| occurrences (all) | 26 | 13 | |

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