



## Clinical trial results:

### A Phase 2, Single-Blind, Controlled, Randomized Study of the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine ± OMV When Administered at an 0-2-6-Month Schedule in Healthy Adolescents 11-18 Years of Age.

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

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004734-25 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 10 April 2007  |

## Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v2 (current)  |
| This version publication date  | 12 June 2016  |
| First version publication date | 19 March 2015 |
| Version creation reason        |               |

## Trial information

### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | V72P3 |
|-----------------------|-------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00297817 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                                                |
|------------------------------|--------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Vaccines and Diagnostics S.r.l                                        |
| Sponsor organisation address | Via Fiorentina,, Siena, Italy, 53100                                           |
| Public contact               | Posting Director, Novartis Vaccines,<br>RegistryContactVaccinesUS@novartis.com |
| Scientific contact           | Posting Director, Novartis Vaccines,<br>RegistryContactVaccinesUS@novartis.com |

Notes:

## Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 06 September 2007 |
| Is this the analysis of the primary completion data? | No                |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 10 April 2007 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

To explore the immunogenicity of two and three doses of rMenB ± OMV in healthy adolescents at 1 month after the second and third doses, by evaluation of the breadth of bactericidal activity (measured by bactericidal complement assay [BCA]) response against a panel of genetically distinct meningococcal strains.

Protection of trial subjects:

Study vaccines were not administered to individuals with known hypersensitivity to any component of the vaccines. An oral temperature  $\geq 38.0^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ) or serious active infection was a reason for delaying vaccination. Standard immunization practices were observed and care was taken to administer the injection intramuscularly. As with all injectable vaccines, appropriate medical treatment and supervision was readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 and diphenhydramine was available in case of any anaphylactic reactions. Care was taken to ensure that the vaccine is not injected into a blood vessel.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 07 February 2006 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 203 |
| Worldwide total number of subjects   | 203                |
| 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)                     | 15  |
| Adolescents (12-17 years)                 | 172 |

|                      |    |
|----------------------|----|
| Adults (18-64 years) | 16 |
| From 65 to 84 years  | 0  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled from 8 centres in the United States

### Pre-assignment

Screening details:

All enrolled subjects were administered the vaccine in accordance with the randomization scheme.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Single blind                   |
| Roles blinded                | Subject                        |

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | rMenB |

Arm description:

Healthy adolescents 11 through 18 years of age administered three doses of rMenB according to a 0, 2, 6-month immunization schedule

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | rMenB                    |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Subjects received 3 doses of 0.5 mL each

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | rMenB + OMV |
|------------------|-------------|

Arm description:

Healthy adolescents 11 through 18 years of age administered three doses of rMenB + OMV according to a 0, 2, 6-month immunization schedule

|                                        |                          |
|----------------------------------------|--------------------------|
| Arm type                               | Experimental             |
| Investigational medicinal product name | rMenB + OMV              |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Subjects received 3 doses of 0.5 mL each

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Healthy adolescents 11 through 18 years of age administered three doses of placebo according to a 0, 2, 6-month immunization schedule

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Saline                 |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intramuscular use      |

Dosage and administration details:

Subjects received 3 doses of 0.5 mL each

| <b>Number of subjects in period 1</b> | rMenB | rMenB + OMV | Placebo |
|---------------------------------------|-------|-------------|---------|
| Started                               | 83    | 79          | 41      |
| Completed                             | 78    | 76          | 40      |
| Not completed                         | 5     | 3           | 1       |
| Consent withdrawn by subject          | 3     | -           | 1       |
| Adverse Event                         | -     | 2           | -       |
| Pregnancy                             | 1     | -           | -       |
| Lost to follow-up                     | -     | 1           | -       |
| Inappropriate Enrollment              | 1     | -           | -       |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                           |             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                                     | rMenB       |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of rMenB according to a 0, 2, 6-month immunization schedule       |             |
| Reporting group title                                                                                                                                                     | rMenB + OMV |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of rMenB + OMV according to a 0, 2, 6-month immunization schedule |             |
| Reporting group title                                                                                                                                                     | Placebo     |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of placebo according to a 0, 2, 6-month immunization schedule     |             |

| Reporting group values                                                                                                                                                                                                                                    | rMenB | rMenB + OMV | Placebo |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------|---------|
| Number of subjects                                                                                                                                                                                                                                        | 83    | 79          | 41      |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |       |             |         |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |       |             |         |
| Age continuous<br>Units: years                                                                                                                                                                                                                            |       |             |         |
| arithmetic mean                                                                                                                                                                                                                                           | 14.3  | 14.4        | 14.8    |
| standard deviation                                                                                                                                                                                                                                        | ± 2.1 | ± 1.9       | ± 2     |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                     |       |             |         |
| Female                                                                                                                                                                                                                                                    | 36    | 35          | 18      |
| Male                                                                                                                                                                                                                                                      | 47    | 44          | 23      |

| Reporting group values                                                                                                                                      | Total                 |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--|--|
| Number of subjects                                                                                                                                          | 203                   |  |  |
| Age categorical<br>Units: Subjects                                                                                                                          |                       |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years) | 0<br>0<br>0<br>0<br>0 |  |  |

|                           |     |  |  |
|---------------------------|-----|--|--|
| Adolescents (12-17 years) | 0   |  |  |
| Adults (18-64 years)      | 0   |  |  |
| From 65-84 years          | 0   |  |  |
| 85 years and over         | 0   |  |  |
| Age continuous            |     |  |  |
| Units: years              |     |  |  |
| arithmetic mean           |     |  |  |
| standard deviation        | -   |  |  |
| Gender categorical        |     |  |  |
| Units: Subjects           |     |  |  |
| Female                    | 89  |  |  |
| Male                      | 114 |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | rMenB                                  |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of rMenB according to a 0, 2, 6-month immunization schedule                                                                                                                                                                                                                                                                                                                          |                                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | rMenB + OMV                            |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of rMenB + OMV according to a 0, 2, 6-month immunization schedule                                                                                                                                                                                                                                                                                                                    |                                        |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Placebo                                |
| Reporting group description:<br>Healthy adolescents 11 through 18 years of age administered three doses of placebo according to a 0, 2, 6-month immunization schedule                                                                                                                                                                                                                                                                                                                        |                                        |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Enrolled population                    |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Intention-to-treat                     |
| Subject analysis set description:<br>All subjects enrolled in the study.                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Modified Intention-to-treat population |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Modified intention-to-treat            |
| Subject analysis set description:<br>All randomized subjects who received the vaccine, and provided at least one evaluable serum sample before and one after vaccination                                                                                                                                                                                                                                                                                                                     |                                        |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Per protocol population                |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Per protocol                           |
| Subject analysis set description:<br>All subjects in the MITT Set who received all the relevant doses of vaccine correctly, and provided evaluable serum samples at the relevant timepoints, and had no major protocol violation as defined prior to unblinding. A "major" deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity results of the subject compared to the result that would have possibly otherwise been obtained |                                        |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Safety population                      |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Safety analysis                        |
| Subject analysis set description:<br>All subjects who were injected and who had post-injection safety data                                                                                                                                                                                                                                                                                                                                                                                   |                                        |

### Primary: Percentage of subjects with bactericidal titers $\geq 1:4$ prior to the 1st and at 1 month after the 2nd and 3rd vaccination.

|                                                                                                                                                                                                                                                                                                                          |                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                          | Percentage of subjects with bactericidal titers $\geq 1:4$ prior to the 1st and at 1 month after the 2nd and 3rd vaccination. <sup>[1]</sup> |
| End point description:<br>Bactericidal activity as measured by the percentage of subjects achieving BCA titers $\geq 1:4$ against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) prior to the 1st and 1 month after the 2nd and 3rd doses of either rMenB, rMenB + OMV or placebo |                                                                                                                                              |
| End point type                                                                                                                                                                                                                                                                                                           | Primary                                                                                                                                      |
| End point timeframe:<br>Pre 1st vaccination, 1 month after 2nd vaccination, 1 month after 3rd vaccination                                                                                                                                                                                                                |                                                                                                                                              |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: there is no statistical analysis for this endpoint.



| End point values                                   | rMenB           | rMenB + OMV     | Placebo         |  |
|----------------------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                                 | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                        | 40              | 38              | 23              |  |
| Units: Percentage of subjects                      |                 |                 |                 |  |
| number (confidence interval 95%)                   |                 |                 |                 |  |
| 44/76-SL (Pre 1st vaccination)                     | 3 (0.063 to 13) | 11 (3 to 25)    | 4 (0 to 22)     |  |
| 44/76-SL (1 month after 2nd vaccination)           | 98 (87 to 100)  | 100 (91 to 100) | 4 (0 to 22)     |  |
| 44/76-SL(1 month after 3rd vaccination)N= 38,37,23 | 100 (91 to 100) | 100 (91 to 100) | 4 (0 to 22)     |  |
| 5/99 (Pre 1st vaccination)                         | 5 (1 to 17)     | 16 (6 to 31)    | 0 (0 to 15)     |  |
| 5/99 (1 month after 2nd vaccination)               | 100 (91 to 100) | 100 (91 to 100) | 0 (0 to 15)     |  |
| 5/99(1 month after 3rd vaccination)N=39,37,23      | 100 (91 to 100) | 100 (91 to 100) | 0 (0 to 15)     |  |
| GB013(Pre 1st vaccination)N=39,38,23               | 5 (1 to 17)     | 11 (3 to 25)    | 4 (0 to 22)     |  |
| GB013 (1 month after 2nd vaccination)              | 20 (9 to 36)    | 39 (24 to 57)   | 4 (0 to 22)     |  |
| GB013(1 month after 3rd vaccination)N=37,37,23     | 24 (12 to 41)   | 54 (37 to 71)   | 4 (0 to 22)     |  |
| NZ98/254(Pre 1st vaccination)N=39,38,23            | 0 (0 to 9)      | 8 (2 to 21)     | 0 (0 to 15)     |  |
| NZ98/254(1 month after 2nd vaccination)            | 10 (3 to 24)    | 50 (33 to 67)   | 0 (0 to 15)     |  |
| NZ98/254(1 month after 3rd vaccination)N=37,37,23  | 51 (34 to 68)   | 76 (59 to 88)   | 0 (0 to 15)     |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of subjects with bactericidal titers $\geq 1:4$ at 4 months after the 2nd and 6 months after the 3rd vaccination

|                 |                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects with bactericidal titers $\geq 1:4$ at 4 months after the 2nd and 6 months after the 3rd vaccination <sup>[2]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the percentage of subjects achieving BCA titers  $\geq 1:4$  against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) at 4 months after the 2nd and 6 months after the 3rd dose of either rMenB, rMenB + OMV or placebo

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

End point timeframe:

4 months after the 2nd vaccination, 6 months after the 3rd vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: there is no statistical analysis for this endpoint.

| End point values                          | rMenB           | rMenB + OMV     | Placebo         |  |
|-------------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                        | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed               | 40              | 38              | 23              |  |
| Units: Percentage of subjects             |                 |                 |                 |  |
| arithmetic mean (confidence interval 95%) |                 |                 |                 |  |

|                                                    |                 |                 |             |  |
|----------------------------------------------------|-----------------|-----------------|-------------|--|
| 44/76-SL (4 months after 2nd vaccination)          | 70 (53 to 83)   | 87 (72 to 96)   | 9 (1 to 28) |  |
| 44/76-SL(6 months after 3rd vaccination)N=39,38,23 | 59 (42 to 74)   | 87 (72 to 96)   | 9 (1 to 28) |  |
| 5/99 (4 months after 2nd vaccination)              | 100 (91 to 100) | 100 (91 to 100) | 4 (0 to 22) |  |
| 5/99 (6 months after 3rd vaccination)              | 100 (91 to 100) | 100 (91 to 100) | 9 (1 to 28) |  |
| GB013 (4 months after 2nd vaccination)             | 5 (1 to 17)     | 24 (11 to 40)   | 0 (0 to 15) |  |
| GB013(6 months after 3rd vaccination)N=39,38,23    | 8 (2 to 21)     | 29 (15 to 46)   | 9 (1 to 28) |  |
| NZ98/254 (4 months after 2nd vaccination)          | 3 (0.063 to 13) | 21 (10 to 37)   | 0 (0 to 15) |  |
| NZ98/254(6 months after 3rd vaccination)N=39,38,23 | 3 (0.065 to 13) | 18 (8 to 34)    | 4 (0 to 22) |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of subjects with bactericidal titers $\geq 1:4$ at 7 days after the 3rd vaccination

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects with bactericidal titers $\geq 1:4$ at 7 days after the 3rd vaccination <sup>[3]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the percentage of subjects that achieving BCA titers  $\geq 1:4$  against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) at 7 days after the 3rd dose of either rMenB, rMenB + OMV or placebo.

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

End point timeframe:

7 days after the 3rd vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: there is no statistical analysis for this endpoint.

| End point values                 | rMenB           | rMenB + OMV     | Placebo         |  |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type               | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed      | 9               | 10              | 6               |  |
| Units: Percentage of subjects    |                 |                 |                 |  |
| number (confidence interval 95%) |                 |                 |                 |  |
| 44/76-SL                         | 89 (52 to 100)  | 90 (55 to 100)  | 0 (0 to 46)     |  |
| 5/99                             | 100 (66 to 100) | 90 (55 to 100)  | 17 (0 to 64)    |  |
| GB013                            | 0 (0 to 34)     | 30 (7 to 65)    | 17 (0 to 64)    |  |
| NZ98/254                         | 22 (3 to 60)    | 40 (12 to 74)   | 0 (0 to 46)     |  |

## Statistical analyses

**Secondary: BCA geometric mean titers prior to the 1st and at 1 month after the 2nd and 3rd vaccination**

|                                                                                                                                                                                                                                                                |                                                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                | BCA geometric mean titers prior to the 1st and at 1 month after the 2nd and 3rd vaccination |
| End point description:<br>Bactericidal activity as measured by GMTs against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) prior to the 1st and 1 month after 2nd and 3rd doses of either rMenB, rMenB + OMV or placebo |                                                                                             |
| End point type                                                                                                                                                                                                                                                 | Secondary                                                                                   |
| End point timeframe:<br>Pre 1st vaccination, 1 month after 2nd vaccination, 1 month after 3rd vaccination                                                                                                                                                      |                                                                                             |

| End point values                                  | rMenB               | rMenB + OMV         | Placebo             |  |
|---------------------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                       | 40                  | 38                  | 23                  |  |
| Units: Titers                                     |                     |                     |                     |  |
| geometric mean (confidence interval 95%)          |                     |                     |                     |  |
| 44/76-SL (Pre 1st vaccination)                    | 1.06 (0.87 to 1.28) | 1.35 (1.11 to 1.64) | 1.1 (0.86 to 1.42)  |  |
| 44/76-SL (1 month after 2nd vaccination)          | 48 (37 to 62)       | 102 (78 to 134)     | 1.1 (0.78 to 1.56)  |  |
| 44/76-SL(1 month after 3rd vaccination)N=38,37,23 | 115 (89 to 150)     | 134 (103 to 175)    | 1.1 (0.79 to 1.53)  |  |
| 5/99 (Pre 1st vaccination)                        | 1.23 (0.92 to 1.65) | 1.63 (1.21 to 2.2)  | 1.13 (0.77 to 1.66) |  |
| 5/99 (1 month after 2nd vaccination)              | 359 (288 to 449)    | 365 (291 to 458)    | 1.17 (0.88 to 1.56) |  |
| 5/99(1 month after 3rd vaccination)N=39,37,23     | 956 (776 to 1179)   | 658 (531 to 816)    | 1.11 (0.85 to 1.46) |  |
| GB013(Pre 1st vaccination)N=39,38,23              | 1.17 (0.96 to 1.42) | 1.31 (1.08 to 1.59) | 1.13 (0.88 to 1.45) |  |
| GB013 (1 month after 2nd vaccination)             | 1.5 (1.12 to 2.01)  | 3.26 (2.42 to 4.39) | 1.13 (0.78 to 1.66) |  |
| GB013(1 month after 3rd vaccination)N=37,37,23    | 1.63 (1.18 to 2.24) | 3.75 (2.72 to 5.16) | 1.09 (0.73 to 1.63) |  |
| NZ98/254(Pre 1st vaccination)N=39,38,23           | 1.04 (0.89 to 1.21) | 1.26 (1.08 to 1.46) | 1.03 (0.85 to 1.25) |  |
| NZ98/254 (1 month after 2nd vaccination)          | 1.25 (0.85 to 1.82) | 4.62 (3.13 to 6.82) | 1.03 (0.62 to 1.69) |  |
| NZ98/254(1 month after 3rd vaccination)N=37,37,23 | 4.3 (2.74 to 6.75)  | 9.56 (6.1 to 15)    | 1.11 (0.63 to 1.94) |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: BCA geometric mean ratio to baseline at 1 month after the second and third vaccination**

|                                                                                                                                                                                                         |                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                         | BCA geometric mean ratio to baseline at 1 month after the second and third vaccination |
| End point description:<br>Bactericidal activity as measured by the ratio between BCA geometric mean titers at 1 months after the 2nd and 3rd doses of either rMenB, rMenB + OMV or placebo and baseline |                                                                                        |
| End point type                                                                                                                                                                                          | Secondary                                                                              |
| End point timeframe:<br>1 month after 2nd vaccination, 1 month after 3rd vaccination                                                                                                                    |                                                                                        |

| End point values                                  | rMenB               | rMenB + OMV         | Placebo             |  |
|---------------------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                                | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                       | 40                  | 38                  | 23                  |  |
| Units: Ratio of GMTs                              |                     |                     |                     |  |
| geometric mean (confidence interval 95%)          |                     |                     |                     |  |
| 44/76-SL(1 month after 2nd vacc/prevaccination)   | 45 (33 to 62)       | 76 (55 to 104)      | 1 (0.67 to 1.5)     |  |
| 44/76-SL(1 month after 3rd vaccination)N=38,37,23 | 114 (84 to 155)     | 98 (72 to 134)      | 0.99 (0.67 to 1.46) |  |
| 5/99(1 month after 2nd vacc/prevaccination)       | 292 (209 to 410)    | 224 (159 to 315)    | 1.03 (0.67 to 1.6)  |  |
| 5/99(1 month after 3rd vaccination)N=39,37,23     | 777 (542 to 1112)   | 400 (277 to 579)    | 0.98 (0.62 to 1.56) |  |
| GB013 (1 month after 2nd vacc/prevaccination)     | 1.31 (1.04 to 1.65) | 2.48 (1.96 to 3.13) | 1 (0.74 to 1.35)    |  |
| GB013(1 month after 3rd vaccination)N=36,37,23    | 1.41 (1.08 to 1.83) | 2.85 (2.19 to 3.7)  | 0.96 (0.69 to 1.34) |  |
| NZ98/254 (1 month after 2nd vaccination)          | 1.21 (0.85 to 1.72) | 3.67 (2.57 to 5.25) | 1 (0.63 to 1.58)    |  |
| NZ98/254(1 month after 3rd vaccination)N=36,37,23 | 4.38 (2.79 to 6.87) | 7.66 (4.91 to 12)   | 1.07 (0.61 to 1.86) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentages of subjects with four-fold rise in bactericidal titers from baseline at 1 month after the second and third vaccination.

|                                                                                                                                                                                                                                                  |                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                  | Percentages of subjects with four-fold rise in bactericidal titers from baseline at 1 month after the second and third vaccination. |
| End point description:<br>Bactericidal activity as measured by the percentage of subjects that achieved a four-fold rise in BCA titers at 1 month after the 2nd and 3rd doses of either rMenB, rMenB + OMV or placebo when compared to baseline. |                                                                                                                                     |
| End point type                                                                                                                                                                                                                                   | Secondary                                                                                                                           |
| End point timeframe:<br>1 month after 2nd vaccination, 1 month after 3rd vaccination                                                                                                                                                             |                                                                                                                                     |

| End point values                                  | rMenB           | rMenB + OMV     | Placebo         |  |
|---------------------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                                | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                       | 40              | 38              | 23              |  |
| Units: Percentage of subjects                     |                 |                 |                 |  |
| number (confidence interval 95%)                  |                 |                 |                 |  |
| 44/76-SL(1 month after 2nd vaccination)           | 95 (83 to 99)   | 97 (86 to 100)  | 0 (0 to 15)     |  |
| 44/76-SL(1month after 3rdvaccination)N=39,38,23   | 100 (91 to 100) | 97 (86 to 100)  | 0 (0 to 15)     |  |
| 5/99 (1 month after 2nd vaccination)              | 100 (91 to 100) | 100 (91 to 100) | 0 (0 to 15)     |  |
| 5/99 (1 month after 3rd vaccination)              | 100 (91 to 100) | 100 (91 to 100) | 0 (0 to 15)     |  |
| GB013(1 month after 2nd vaccination)N=39,38,23    | 3 (0.065 to 13) | 16 (6 to 31)    | 0 (0 to 15)     |  |
| GB013(1 month after 3rd vaccination)N=37,38,23    | 5 (1 to 18)     | 24 (11 to 40)   | 0 (0 to 15)     |  |
| NZ98/254(1 month after 2nd vaccination)N=39,38,23 | 10 (3 to 24)    | 34 (20 to 51)   | 0 (0 to 15)     |  |
| NZ98/254(1 month after 3rd vaccination)N=37,38,23 | 51 (34 to 68)   | 58 (41 to 74)   | 0 (0 to 15)     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: BCA geometric mean titers at 4 month after the 2nd and 6 months after the 3rd vaccination

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | BCA geometric mean titers at 4 month after the 2nd and 6 months after the 3rd vaccination |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by GMTs against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) at 4 months after the 2nd dose and 6 months after the 3rd dose of either rMenB, rMenB + OMV or placebo

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

End point timeframe:

4 months after the 2nd vaccination, 6 months after the 3rd vaccination

| End point values                         | rMenB             | rMenB + OMV     | Placebo            |  |
|------------------------------------------|-------------------|-----------------|--------------------|--|
| Subject group type                       | Reporting group   | Reporting group | Reporting group    |  |
| Number of subjects analysed              | 40                | 38              | 23                 |  |
| Units: Titers                            |                   |                 |                    |  |
| geometric mean (confidence interval 95%) |                   |                 |                    |  |
| 44/76-SL(4 months after 2nd vaccination) | 7.42 (5.04 to 11) | 14 (9.12 to 20) | 1.32 (0.8 to 2.18) |  |

|                                                    |                     |                     |                     |  |
|----------------------------------------------------|---------------------|---------------------|---------------------|--|
| 44/76-SL(6 months after 3rd vaccination)N=39,38,23 | 5.25 (3.6 to 7.64)  | 14 (9.34 to 20)     | 1.24 (0.76 to 2)    |  |
| 5/99 (4 months after 2nd vaccination)              | 122 (89 to 167)     | 101 (73 to 138)     | 1.42 (0.94 to 2.13) |  |
| 5/99 (6 months after 3rd vaccination)              | 227 (169 to 304)    | 135 (101 to 182)    | 1.38 (0.95 to 2.03) |  |
| GB013 (4 months after 2nd vaccination)             | 1.22 (0.95 to 1.55) | 1.93 (1.51 to 2.46) | 1.08 (0.78 to 1.47) |  |
| GB013(6 months after 3rd vaccination)N=39,38,23    | 1.27 (0.98 to 1.63) | 2.13 (1.65 to 2.75) | 1.21 (0.87 to 1.68) |  |
| NZ98/254 (4 months after 2nd vaccination)          | 1.09 (0.82 to 1.44) | 2.03 (1.52 to 2.72) | 1.04 (0.72 to 1.51) |  |
| NZ98/254(6 months after 3rd vaccination)N=38,39,23 | 1.12 (0.83 to 1.49) | 2.01 (1.5 to 2.69)  | 1.22 (0.84 to 1.77) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: BCA geometric mean ratio to baseline at 4 months after the 2nd vaccination and 6 months after the 3rd vaccination

|                 |                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | BCA geometric mean ratio to baseline at 4 months after the 2nd vaccination and 6 months after the 3rd vaccination |
|-----------------|-------------------------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the ratio between BCA geometric mean titers at 4 months after the 2nd and at 6 months after the 3rd dose of either rMenB, rMenB + OMV or placebo and baseline

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

End point timeframe:

4 months after the 2nd vaccination, 6 months after the 3rd vaccination

| End point values                                   | rMenB               | rMenB + OMV         | Placebo             |  |
|----------------------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                                 | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                        | 40                  | 38                  | 23                  |  |
| Units: Ratio of GMTs                               |                     |                     |                     |  |
| geometric mean (confidence interval 95%)           |                     |                     |                     |  |
| 44/76-SL(4 months after 2nd vacc/prevaccination)   | 7.02 (4.7 to 10)    | 10 (6.67 to 15)     | 1.19 (0.71 to 2.01) |  |
| 44/76-SL(6months after 3rdvacc/prevaccn)N=39,38,23 | 4.97 (3.36 to 7.36) | 10 (6.83 to 15)     | 1.12 (0.68 to 1.86) |  |
| 5/99 (4 months after 2nd vacc/prevaccination)      | 99 (68 to 145)      | 62 (42 to 91)       | 1.25 (0.77 to 2.04) |  |
| 5/99(6months after 3rdvacc/prevaccn)N=40,38,23     | 185 (124 to 275)    | 83 (55 to 125)      | 1.22 (0.73 to 2.06) |  |
| GB013(4months after 2ndvacc/prevaccn)N=39,38,23    | 1.05 (0.88 to 1.26) | 1.47 (1.22 to 1.77) | 0.95 (0.75 to 1.2)  |  |
| GB013(6months after 3rdvacc/prevaccn)N=38,38,23    | 1.09 (0.9 to 1.33)  | 1.62 (1.34 to 1.97) | 1.07 (0.84 to 1.37) |  |
| NZ98/254(4months after 2ndvacc/prevaccn)N=39,38,23 | 1.05 (0.85 to 1.31) | 1.62 (1.3 to 2.01)  | 1.01 (0.77 to 1.34) |  |
| NZ98/254(6months after 3rdvacc/prevaccn)N=38,38,23 | 1.12 (0.89 to 1.4)  | 1.6 (1.28 to 2)     | 1.18 (0.89 to 1.57) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentages of subjects with four-fold rise in bactericidal titers from baseline at 4 months after the 2nd and 6 months after the 3rd vaccination

|                 |                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentages of subjects with four-fold rise in bactericidal titers from baseline at 4 months after the 2nd and 6 months after the 3rd vaccination |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the percentage of subjects that achieved a four-fold rise in BCA titers at 4 months after the 2nd dose and at 6 months after the 3rd dose of either rMenB, rMenB+ OMV or placebo when compared to baseline

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

End point timeframe:

4 months after the 2nd vaccination, 6 months after the 3rd vaccination

| End point values                                   | rMenB           | rMenB + OMV     | Placebo         |  |
|----------------------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                                 | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                        | 40              | 38              | 23              |  |
| Units: Percentage of subjects                      |                 |                 |                 |  |
| number (confidence interval 95%)                   |                 |                 |                 |  |
| 44/76-SL (4 months after 2nd vaccination)          | 63 (46 to 77)   | 66 (49 to 80)   | 4 (0 to 22)     |  |
| 44/76-SL(6 months after 3rd vaccination)N=38,37,23 | 45 (29 to 62)   | 73 (56 to 86)   | 4 (0 to 22)     |  |
| 5/99 (4 months after 2nd vaccination)              | 100 (91 to 100) | 95 (82 to 99)   | 4 (0 to 22)     |  |
| 5/99(6 months after 3rd vaccination)N=39,37,23     | 100 (91 to 100) | 95 (82 to 99)   | 9 (1 to 28)     |  |
| GB013(4 months after 2nd vaccination)N=39,38,23    | 0 (0 to 9)      | 5 (1 to 18)     | 0 (0 to 15)     |  |
| GB013(6 months after 3rd vaccination)N=37,37,23    | 0 (0 to 9)      | 8 (2 to 22)     | 4 (0 to 22)     |  |
| NZ98/254(4 months after 2nd vaccination)N=39,38,23 | 0 (0 to 9)      | 11 (3 to 25)    | 0 (0 to 15)     |  |
| NZ98/254(6 months after 3rd vaccination)N=37,37,23 | 0 (0 to 9)      | 14 (5 to 29)    | 4 (0 to 22)     |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: BCA geometric mean ratio to pre-3rd vaccination at 6 months after the 3rd vaccination.**

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|                 |                                                                                        |
|-----------------|----------------------------------------------------------------------------------------|
| End point title | BCA geometric mean ratio to pre-3rd vaccination at 6 months after the 3rd vaccination. |
|-----------------|----------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the ratio between BCA geometric mean titers at 6 months after the 3rd dose of either rMenB, rMenB + OMV or placebo and pre-3rd vaccination.

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

End point timeframe:

6 months after the 3rd vaccination

---

| End point values                         | rMenB               | rMenB + OMV         | Placebo             |  |
|------------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed              | 40                  | 38                  | 23                  |  |
| Units: Ratio of GMTs                     |                     |                     |                     |  |
| geometric mean (confidence interval 95%) |                     |                     |                     |  |
| 44/76-SL (N=39,38,23)                    | 0.73 (0.53 to 1.01) | 1.01 (0.84 to 1.17) | 0.94 (0.62 to 1.43) |  |
| 5/99                                     | 1.86 (1.28 to 2.7)  | 1.35 (0.73 to 1.4)  | 0.98 (0.6 to 1.59)  |  |
| GB013 (N=39,38,23)                       | 1.04 (0.87 to 1.24) | 1.11 (0.92 to 1.97) | 1.13 (0.9 to 1.42)  |  |
| NZ98/254 (N=39,38,23)                    | 1.03 (0.87 to 1.22) | 0.99 (0.92 to 1.33) | 1.17 (0.94 to 1.45) |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentages of subjects with four-fold rise in bactericidal titers from pre-3rd vaccination to 6 months after the 3rd vaccination.**

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|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentages of subjects with four-fold rise in bactericidal titers from pre-3rd vaccination to 6 months after the 3rd vaccination. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the percentage of subjects that achieved a four-fold rise in BCA titers at 6 months after the 3rd dose of either rMenB, rMenB+ OMV or placebo when compared to pre-3rd vaccination

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

End point timeframe:

6 months after the 3rd vaccination

---



| End point values                 | rMenB           | rMenB + OMV     | Placebo         |  |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type               | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed      | 40              | 38              | 23              |  |
| Units: Percentage of subjects    |                 |                 |                 |  |
| number (confidence interval 95%) |                 |                 |                 |  |
| 44/76-SL (N=39,38,23)            | 5 (1 to 17)     | 5 (1 to 18)     | 4 (0 to 23)     |  |
| 5/99                             | 18 (7 to 33)    | 13 (4 to 28)    | 9 (1 to 28)     |  |
| GB013 (N=39,38,23)               | 0 (0 to 9)      | 3 (0.067 to 14) | 4 (0 to 22)     |  |
| NZ98/254 (N=39,38,23)            | 0 (0 to 9)      | 3 (0.067 to 14) | 4 (0 to 22)     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with bactericidal titers $\geq 1:4$ at 7 days after the 3rd vaccination

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects with bactericidal titers $\geq 1:4$ at 7 days after the 3rd vaccination |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the percentage of subjects that achieving BCA titers  $\geq 1:4$  against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) at 7 days after the 3rd dose of either rMenB, rMenB + OMV or placebo.

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

End point timeframe:

7 days after the 3rd vaccination

| End point values                 | rMenB           | rMenB + OMV     | Placebo         |  |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type               | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed      | 9               | 10              | 6               |  |
| Units: Percentage of subjects    |                 |                 |                 |  |
| number (confidence interval 95%) |                 |                 |                 |  |
| 44/76-SL                         | 89 (52 to 100)  | 90 (55 to 100)  | 0 (0 to 46)     |  |
| 5/99                             | 100 (66 to 100) | 90 (55 to 100)  | 17 (0 to 64)    |  |
| GB013                            | 0 (0 to 34)     | 30 (7 to 65)    | 17 (0 to 22)    |  |
| NZ98/254                         | 22 (3 to 60)    | 40 (12 to 74)   | 0 (0 to 46)     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: BCA geometric mean titers at 7 days after the 3rd vaccination

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | BCA geometric mean titers at 7 days after the 3rd vaccination |
|-----------------|---------------------------------------------------------------|

End point description:

Bactericidal activity as measured by GMTs against a panel of genetically distinct meningococcal strains (H44/76, 5/99, GB013, NZ98/254) at 7 days after the 3rd dose of either rMenB, rMenB + OMV or placebo.

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

End point timeframe:

7 days after the 3rd vaccination

| End point values                 | rMenB               | rMenB + OMV         | Placebo             |  |
|----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type               | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed      | 9                   | 10                  | 6                   |  |
| Units: Titers                    |                     |                     |                     |  |
| number (confidence interval 95%) |                     |                     |                     |  |
| 44/76-SL                         | 33 (14 to 79)       | 60 (26 to 137)      | 1 (0.35 to 2.88)    |  |
| 5/99                             | 686 (253 to 1858)   | 367 (142 to 951)    | 1.26 (0.37 to 4.26) |  |
| GB013                            | 1.05 (0.7 to 1.57)  | 1.96 (1.33 to 2.89) | 1.47 (0.89 to 2.41) |  |
| NZ98/254                         | 1.74 (0.93 to 3.23) | 2.76 (1.53 to 4.98) | 1 (0.47 to 2.13)    |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: BCA geometric mean ratio to baseline at 7 days after the 3rd vaccination.

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | BCA geometric mean ratio to baseline at 7 days after the 3rd vaccination. |
|-----------------|---------------------------------------------------------------------------|

End point description:

Bactericidal activity as measured by the ratio between BCA geometric mean titers at 7 days after the 3rd dose of either rMenB, rMenB + OMV or placebo and baseline

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

End point timeframe:

7 days after the 3rd vaccination

| End point values                         | rMenB           | rMenB + OMV     | Placebo          |  |
|------------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                       | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed              | 9               | 10              | 6                |  |
| Units: Ratio of GMTs                     |                 |                 |                  |  |
| geometric mean (confidence interval 95%) |                 |                 |                  |  |
| 44/76-SL                                 | 33 (14 to 79)   | 60 (26 to 137)  | 1 (0.35 to 2.88) |  |

|          |                     |                     |                     |  |
|----------|---------------------|---------------------|---------------------|--|
| 5/99     | 697 (245 to 1986)   | 278 (102 to 754)    | 1.05 (0.29 to 3.77) |  |
| GB013    | 1.06 (0.79 to 1.43) | 2 (1.5 to 2.67)     | 0.95 (0.65 to 1.37) |  |
| NZ98/254 | 1.74 (0.93 to 3.23) | 2.76 (1.53 to 4.98) | 1 (0.47 to 2.13)    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: ELISA GMCs pre-1st vaccination, at 1 month after the 2nd and 3rd dose, and at 4 months after the 2nd and 6 months after the 3rd vaccination

|                 |                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | ELISA GMCs pre-1st vaccination, at 1 month after the 2nd and 3rd dose, and at 4 months after the 2nd and 6 months after the 3rd vaccination |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Induction of specific antibody responses against antigens 287-953, 936-741, 961 and OMV-NW as measuring by enzyme-linked immunosorbent assay (ELISA) geometric mean concentrations (GMCs) in subjects receiving either rMenB, rMenB + OMV or placebo.

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

End point timeframe:

Pre 1st vaccination, at 1 month after the 2nd and 3rd dose, and at 4 months after the 2nd and 6 months after the 3rd vaccination

| End point values                                       | rMenB                  | rMenB + OMV            | Placebo           |  |
|--------------------------------------------------------|------------------------|------------------------|-------------------|--|
| Subject group type                                     | Reporting group        | Reporting group        | Reporting group   |  |
| Number of subjects analysed                            | 40                     | 38                     | 23                |  |
| Units: IU/mL                                           |                        |                        |                   |  |
| geometric mean (confidence interval 95%)               |                        |                        |                   |  |
| 287-953 antigen Pre 1st vaccination                    | 14 (7.72 to 24)        | 19 (11 to 35)          | 13 (5.98 to 26)   |  |
| 287-953 antigen 1 month after 2nd vaccination          | 1643 (1120 to 2410)    | 2847 (1928 to 4204)    | 11 (6.71 to 18)   |  |
| 287-953 antigen 4 months after 2nd vaccination         | 427 (273 to 667)       | 606 (385 to 954)       | 11 (6.25 to 20)   |  |
| 287-953 antigen 1 month after 3 vaccination N=39,37,23 | 2945 (2012 to 4310)    | 3428 (2318 to 5071)    | 8.42 (5.15 to 14) |  |
| 287-953 antigen 6 months after 3rd vaccination         | 852 (582 to 1247)      | 1056 (717 to 1558)     | 18 (11 to 29)     |  |
| 936-741 antigen Pre 1st vaccination                    | 54 (41 to 71)          | 82 (62 to 110)         | 43 (30 to 62)     |  |
| 936-741 antigen 1 month after 2nd vaccination          | 5279 (4064 to 6857)    | 10253 (7857 to 13381)  | 85 (60 to 120)    |  |
| 936-741 antigen 4 months after 2nd vaccination         | 2183 (1663 to 2864)    | 3305 (2506 to 4358)    | 76 (53 to 108)    |  |
| 936-741 antigen 1 month after 3 vaccination N=39,37,23 | 13638 (11047 to 16838) | 16452 (13249 to 20430) | 64 (48 to 83)     |  |
| 936-741 antigen 6 months after 3rd vaccination         | 3384 (2708 to 4228)    | 4388 (3498 to 5505)    | 63 (47 to 84)     |  |
| 961 antigen Pre 1st vaccination                        | 100 (73 to 136)        | 112 (82 to 154)        | 81 (54 to 122)    |  |

|                                                   |                     |                     |                     |  |
|---------------------------------------------------|---------------------|---------------------|---------------------|--|
| 961 antigen 1 month after 2nd vaccination         | 2133 (1661 to 2738) | 2625 (2036 to 3386) | 109 (79 to 151)     |  |
| 961 antigen 4 months after 2nd vaccination        | 919 (708 to 1194)   | 839 (643 to 1094)   | 88 (63 to 124)      |  |
| 961 antigen 1 month after 3vaccination N=39,37,23 | 4029 (3263 to 4975) | 3757 (3025 to 4666) | 83 (63 to 109)      |  |
| 961 antigen 6 months after 3rd vaccination        | 1845 (1504 to 2263) | 1437 (1167 to 1769) | 144 (110 to 188)    |  |
| OMV-NW Pre 1st vaccination                        | 4.29 (2.87 to 6.4)  | 7.3 (4.86 to 11)    | 5.36 (3.18 to 9.03) |  |
| OMV-NW 1 month after 2nd vaccination              | 8.64 (5.58 to 13)   | 522 (334 to 814)    | 6.42 (3.63 to 11)   |  |
| OMV-NW 4 months after 2nd vaccination             | 15 (11 to 22)       | 103 (71 to 150)     | 12 (7.19 to 19)     |  |
| OMV-NW 1 month after 3vaccination N=39,37,23      | 27 (17 to 42)       | 644 (402 to 1030)   | 13 (7.14 to 23)     |  |
| OMV-NW 6 months after 3rd vaccination             | 26 (18 to 39)       | 142 (95 to 213)     | 21 (13 to 35)       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: ELISA GMCs at 7 days after the 3rd vaccination.

|                                                                                                                                                                                                                                                                                |                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                | ELISA GMCs at 7 days after the 3rd vaccination. |
| End point description:<br>Induction of specific antibody responses against antigens 287-953, 936-741, 961 and OMV-NW as measuring by enzyme-linked immunosorbent assay (ELISA) geometric mean concentrations (GMCs) in subjects receiving either rMenB, rMenB + OMV or placebo |                                                 |
| End point type                                                                                                                                                                                                                                                                 | Secondary                                       |
| End point timeframe:<br>7 days after 3rd vaccination                                                                                                                                                                                                                           |                                                 |

| End point values                         | rMenB                | rMenB + OMV          | Placebo           |  |
|------------------------------------------|----------------------|----------------------|-------------------|--|
| Subject group type                       | Reporting group      | Reporting group      | Reporting group   |  |
| Number of subjects analysed              | 9                    | 10                   | 6                 |  |
| Units: IU/mL                             |                      |                      |                   |  |
| geometric mean (confidence interval 95%) |                      |                      |                   |  |
| 287-953 antigen                          | 1316 (450 to 3843)   | 1455 (523 to 4046)   | 3.36 (0.91 to 12) |  |
| 936-741 antigen                          | 9325 (3020 to 28790) | 6161 (2101 to 18065) | 57 (14 to 226)    |  |
| 961 antigen                              | 3114 (1608 to 6031)  | 1912 (1017 to 3592)  | 91 (40 to 203)    |  |
| OMV-NW                                   | 14 (4.44 to 42)      | 157 (54 to 457)      | 20 (5.02 to 78)   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidences of (severe) local and systemic reactions during the 7 days following the 1st vaccination

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Incidences of (severe) local and systemic reactions during the 7 days following the 1st vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

Safety and tolerability of rMenB and rMenB + OMV in healthy adolescents relative to a placebo control arm in terms of number of subjects that experienced (severe) local or systemic solicited adverse events (AEs) or other indicators of reactogenicity during the 7 days following the 1st vaccination

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

End point timeframe:

Day 1 through Day 7

| End point values                     | rMenB           | rMenB + OMV     | Placebo         |  |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed          | 83              | 79              | 41              |  |
| Units: Subjects                      |                 |                 |                 |  |
| Injection site pain                  | 74              | 76              | 9               |  |
| Severe injection site pain           | 6               | 12              | 0               |  |
| Erythema                             | 9               | 30              | 6               |  |
| Severe erythema                      | 0               | 0               | 0               |  |
| Induration                           | 4               | 18              | 0               |  |
| Severe induration                    | 0               | 0               | 0               |  |
| Fever                                | 1               | 0               | 0               |  |
| Severe fever                         | 0               | 0               | 0               |  |
| Chills                               | 15              | 10              | 5               |  |
| Severe chills                        | 1               | 0               | 0               |  |
| Nausea                               | 16              | 18              | 8               |  |
| Severe Nausea                        | 1               | 2               | 2               |  |
| Malaise                              | 24              | 25              | 8               |  |
| Severe malaise                       | 1               | 3               | 2               |  |
| Fatigue                              | 27              | 29              | 12              |  |
| Severe fatigue                       | 1               | 2               | 1               |  |
| Myalgia                              | 23              | 21              | 5               |  |
| Severe myalgia                       | 0               | 1               | 1               |  |
| Arthralgia                           | 12              | 9               | 5               |  |
| Severe arthralgia                    | 0               | 0               | 1               |  |
| Headache                             | 32              | 30              | 12              |  |
| Severe headache                      | 3               | 0               | 1               |  |
| Stayed home due to reaction          | 5               | 5               | 1               |  |
| Analgesic/antipyretic medication use | 23              | 31              | 6               |  |

## Statistical analyses

**Secondary: Incidences of (severe) local and systemic reactions during the 7 days following the 2nd vaccination**

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Incidences of (severe) local and systemic reactions during the 7 days following the 2nd vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

To explore the safety and tolerability of rMenB and rMenB + OMV in healthy adolescents relative to a placebo control arm in terms of number of subjects that experienced (severe) local, or systemic solicited adverse events (AEs) or other indicators of reactogenicity during the 7 days following the 2nd vaccination

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

End point timeframe:

Day 61 through Day 67

| End point values                     | rMenB           | rMenB + OMV     | Placebo         |  |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed          | 81              | 77              | 41              |  |
| Units: Subjects                      |                 |                 |                 |  |
| Injection site pain                  | 60              | 67              | 10              |  |
| Severe injection site pain           | 5               | 12              | 1               |  |
| Erythema                             | 17              | 26              | 8               |  |
| Severe erythema                      | 0               | 0               | 0               |  |
| Induration                           | 11              | 21              | 4               |  |
| Severe induration                    | 0               | 0               | 0               |  |
| Fever                                | 0               | 1               | 0               |  |
| Severe fever                         | 0               | 0               | 0               |  |
| Chills                               | 9               | 11              | 2               |  |
| Severe chills                        | 0               | 3               | 0               |  |
| Nausea                               | 11              | 8               | 3               |  |
| Severe Nausea                        | 0               | 2               | 1               |  |
| Malaise                              | 16              | 18              | 4               |  |
| Severe malaise                       | 0               | 4               | 1               |  |
| Fatigue                              | 28              | 25              | 9               |  |
| Severe fatigue                       | 1               | 3               | 1               |  |
| Myalgia                              | 16              | 20              | 2               |  |
| Severe myalgia                       | 0               | 2               | 1               |  |
| Arthralgia                           | 9               | 17              | 4               |  |
| Severe arthralgia                    | 0               | 2               | 0               |  |
| Headache                             | 21              | 20              | 7               |  |
| Severe headache                      | 1               | 5               | 1               |  |
| Stayed home due to reaction          | 1               | 5               | 0               |  |
| Analgesic/antipyretic medication use | 14              | 21              | 4               |  |

**Statistical analyses**

**Secondary: Incidences of (severe) local and systemic reactions during the 7 days following the 3rd vaccination**

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Incidences of (severe) local and systemic reactions during the 7 days following the 3rd vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

To explore the safety and tolerability of rMenB and rMenB + OMV in healthy adolescents relative to a placebo control arm in terms of number of subjects that experienced (severe) local, or systemic solicited adverse events (AEs) or other indicators of reactogenicity during the 7 days following the 3rd vaccination.

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

End point timeframe:

Day 181 through Day 187

| End point values                     | rMenB           | rMenB + OMV     | Placebo         |  |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed          | 78              | 76              | 40              |  |
| Units: Subjects                      |                 |                 |                 |  |
| Injection site pain                  | 57              | 66              | 6               |  |
| Severe injection site pain           | 6               | 13              | 0               |  |
| Erythema                             | 21              | 23              | 2               |  |
| Severe erythema                      | 1               | 0               | 0               |  |
| Induration                           | 20              | 25              | 0               |  |
| Severe induration                    | 0               | 0               | 0               |  |
| Fever                                | 1               | 0               | 1               |  |
| Severe fever                         | 0               | 0               | 0               |  |
| Chills                               | 4               | 9               | 2               |  |
| Severe chills                        | 0               | 1               | 0               |  |
| Nausea                               | 1               | 7               | 5               |  |
| Severe Nausea                        | 1               | 0               | 0               |  |
| Malaise                              | 10              | 18              | 6               |  |
| Severe malaise                       | 3               | 3               | 0               |  |
| Fatigue                              | 21              | 13              | 7               |  |
| Severe fatigue                       | 1               | 5               | 1               |  |
| Myalgia                              | 13              | 13              | 4               |  |
| Severe myalgia                       | 0               | 3               | 0               |  |
| Arthralgia                           | 6               | 8               | 2               |  |
| Severe arthralgia                    | 0               | 2               | 0               |  |
| Headache                             | 12              | 17              | 6               |  |
| Severe headache                      | 2               | 1               | 0               |  |
| Stayed home due to reaction          | 1               | 1               | 0               |  |
| Analgesic/antipyretic medication use | 11              | 16              | 3               |  |

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Overview of other unsolicited AEs**

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|                 |                                   |
|-----------------|-----------------------------------|
| End point title | Overview of other unsolicited AEs |
|-----------------|-----------------------------------|

End point description:

To explore the safety and tolerability of rMenB and rMenB + OMV in healthy adolescents relative to a placebo control arm in terms of number of subjects that experienced other unsolicited AEs after any vaccination, including possible/probable relationship to the vaccine administered

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

End point timeframe:

Day 1 through study termination

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| End point values                                  | rMenB           | rMenB + OMV     | Placebo         |  |
|---------------------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                                | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                       | 83              | 79              | 41              |  |
| Units: Number of subjects                         |                 |                 |                 |  |
| AE including abnormal laboratory values           | 82              | 78              | 41              |  |
| AE when excluding abnormal laboratory values      | 60              | 50              | 26              |  |
| Atleast possible AE including abnormal lab values | 22              | 25              | 4               |  |
| AEs leading to withdrawal from the study          | 0               | 2               | 0               |  |
| SAE including abnormal laboratory values          | 0               | 1               | 2               |  |
| Atleast possible related SAE abnormal lab values  | 0               | 1               | 0               |  |
| Death                                             | 0               | 0               | 0               |  |

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**Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited local and systemic AEs, oral temperature, all other AEs, and all concomitant medications were collected for 7 days following each vaccination. SAEs and AEs leading to withdrawal from the study were collected throughout the entire study period.

Adverse event reporting additional description:

Solicited local and systemic AEs, oral temperature, all other AEs, and all concomitant medications were collected for 7 days following each vaccination through systematic assessment. SAEs and AEs leading to withdrawal from the study were collected throughout the entire study period through non-systematic assessment.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 9.1    |

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | rMenB |
|-----------------------|-------|

Reporting group description:

Healthy adolescents 11 through 18 years of age administered three doses of rMenB according to a 0, 2, 6-month immunization schedule

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Healthy adolescents 11 through 18 years of age administered three doses of placebo according to a 0, 2, 6-month immunization schedule

|                       |             |
|-----------------------|-------------|
| Reporting group title | rMenB + OMV |
|-----------------------|-------------|

Reporting group description:

Healthy adolescents 11 through 18 years of age administered three doses of rMenB + OMV according to a 0, 2, 6-month immunization schedule

| Serious adverse events                            | rMenB          | Placebo        | rMenB + OMV    |
|---------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 83 (0.00%) | 2 / 41 (4.88%) | 1 / 79 (1.27%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    |                |                |                |
| Injury, poisoning and procedural complications    |                |                |                |
| ALCOHOL POISONING                                 |                |                |                |
| subjects affected / exposed                       | 0 / 83 (0.00%) | 1 / 41 (2.44%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                       |                |                |                |
| APPENDICITIS                                      |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 83 (0.00%) | 0 / 41 (0.00%) | 1 / 79 (1.27%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| <b>PELVIC INFLAMMATORY DISEASE</b>              |                |                |                |
| subjects affected / exposed                     | 0 / 83 (0.00%) | 1 / 41 (2.44%) | 0 / 79 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                      | rMenB             | Placebo           | rMenB + OMV       |
|--------------------------------------------------------|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events  |                   |                   |                   |
| subjects affected / exposed                            | 83 / 83 (100.00%) | 41 / 41 (100.00%) | 79 / 79 (100.00%) |
| <b>Investigations</b>                                  |                   |                   |                   |
| <b>ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED</b> |                   |                   |                   |
| subjects affected / exposed                            | 4 / 83 (4.82%)    | 1 / 41 (2.44%)    | 5 / 79 (6.33%)    |
| occurrences (all)                                      | 6                 | 1                 | 19                |
| <b>ALANINE AMINOTRANSFERASE DECREASED</b>              |                   |                   |                   |
| subjects affected / exposed                            | 20 / 83 (24.10%)  | 9 / 41 (21.95%)   | 13 / 79 (16.46%)  |
| occurrences (all)                                      | 42                | 16                | 26                |
| <b>ALANINE AMINOTRANSFERASE INCREASED</b>              |                   |                   |                   |
| subjects affected / exposed                            | 8 / 83 (9.64%)    | 3 / 41 (7.32%)    | 3 / 79 (3.80%)    |
| occurrences (all)                                      | 13                | 3                 | 4                 |
| <b>BLOOD ALKALINE PHOSPHATASE INCREASED</b>            |                   |                   |                   |
| subjects affected / exposed                            | 3 / 83 (3.61%)    | 1 / 41 (2.44%)    | 4 / 79 (5.06%)    |
| occurrences (all)                                      | 7                 | 2                 | 13                |
| <b>BLOOD BICARBONATE DECREASED</b>                     |                   |                   |                   |
| subjects affected / exposed                            | 7 / 83 (8.43%)    | 4 / 41 (9.76%)    | 8 / 79 (10.13%)   |
| occurrences (all)                                      | 11                | 4                 | 9                 |
| <b>BLOOD BILIRUBIN DECREASED</b>                       |                   |                   |                   |
| subjects affected / exposed                            | 3 / 83 (3.61%)    | 2 / 41 (4.88%)    | 5 / 79 (6.33%)    |
| occurrences (all)                                      | 5                 | 2                 | 8                 |
| <b>BLOOD BILIRUBIN INCREASED</b>                       |                   |                   |                   |

|                                        |                  |                  |                  |
|----------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed            | 1 / 83 (1.20%)   | 3 / 41 (7.32%)   | 0 / 79 (0.00%)   |
| occurrences (all)                      | 3                | 5                | 0                |
| BLOOD CHLORIDE INCREASED               |                  |                  |                  |
| subjects affected / exposed            | 1 / 83 (1.20%)   | 0 / 41 (0.00%)   | 4 / 79 (5.06%)   |
| occurrences (all)                      | 1                | 0                | 4                |
| BLOOD CREATINE PHOSPHOKINASE INCREASED |                  |                  |                  |
| subjects affected / exposed            | 4 / 83 (4.82%)   | 2 / 41 (4.88%)   | 11 / 79 (13.92%) |
| occurrences (all)                      | 6                | 2                | 19               |
| BLOOD CREATININE INCREASED             |                  |                  |                  |
| subjects affected / exposed            | 4 / 83 (4.82%)   | 4 / 41 (9.76%)   | 8 / 79 (10.13%)  |
| occurrences (all)                      | 6                | 4                | 14               |
| BLOOD FIBRINOGEN INCREASED             |                  |                  |                  |
| subjects affected / exposed            | 2 / 83 (2.41%)   | 1 / 41 (2.44%)   | 5 / 79 (6.33%)   |
| occurrences (all)                      | 4                | 1                | 8                |
| BLOOD GLUCOSE INCREASED                |                  |                  |                  |
| subjects affected / exposed            | 7 / 83 (8.43%)   | 3 / 41 (7.32%)   | 5 / 79 (6.33%)   |
| occurrences (all)                      | 10               | 5                | 5                |
| BLOOD LACTATE DEHYDROGENASE INCREASED  |                  |                  |                  |
| subjects affected / exposed            | 5 / 83 (6.02%)   | 1 / 41 (2.44%)   | 0 / 79 (0.00%)   |
| occurrences (all)                      | 7                | 1                | 0                |
| EOSINOPHIL COUNT INCREASED             |                  |                  |                  |
| subjects affected / exposed            | 6 / 83 (7.23%)   | 4 / 41 (9.76%)   | 3 / 79 (3.80%)   |
| occurrences (all)                      | 8                | 4                | 5                |
| FIBRIN D DIMER INCREASED               |                  |                  |                  |
| subjects affected / exposed            | 1 / 83 (1.20%)   | 3 / 41 (7.32%)   | 2 / 79 (2.53%)   |
| occurrences (all)                      | 2                | 7                | 2                |
| HAEMATOCRIT INCREASED                  |                  |                  |                  |
| subjects affected / exposed            | 46 / 83 (55.42%) | 23 / 41 (56.10%) | 41 / 79 (51.90%) |
| occurrences (all)                      | 108              | 54               | 100              |
| HAEMOGLOBIN DECREASED                  |                  |                  |                  |
| subjects affected / exposed            | 3 / 83 (3.61%)   | 0 / 41 (0.00%)   | 4 / 79 (5.06%)   |
| occurrences (all)                      | 3                | 0                | 7                |
| HAEMOGLOBIN INCREASED                  |                  |                  |                  |

|                                    |                  |                  |                  |
|------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed        | 17 / 83 (20.48%) | 11 / 41 (26.83%) | 19 / 79 (24.05%) |
| occurrences (all)                  | 33               | 18               | 40               |
| LYMPHOCYTE COUNT DECREASED         |                  |                  |                  |
| subjects affected / exposed        | 30 / 83 (36.14%) | 20 / 41 (48.78%) | 33 / 79 (41.77%) |
| occurrences (all)                  | 57               | 41               | 68               |
| LYMPHOCYTE COUNT INCREASED         |                  |                  |                  |
| subjects affected / exposed        | 25 / 83 (30.12%) | 8 / 41 (19.51%)  | 26 / 79 (32.91%) |
| occurrences (all)                  | 56               | 14               | 70               |
| MEAN CELL HAEMOGLOBIN<br>DECREASED |                  |                  |                  |
| subjects affected / exposed        | 4 / 83 (4.82%)   | 1 / 41 (2.44%)   | 4 / 79 (5.06%)   |
| occurrences (all)                  | 13               | 5                | 8                |
| MEAN CELL VOLUME INCREASED         |                  |                  |                  |
| subjects affected / exposed        | 16 / 83 (19.28%) | 10 / 41 (24.39%) | 19 / 79 (24.05%) |
| occurrences (all)                  | 31               | 18               | 32               |
| MONOCYTE COUNT INCREASED           |                  |                  |                  |
| subjects affected / exposed        | 14 / 83 (16.87%) | 7 / 41 (17.07%)  | 11 / 79 (13.92%) |
| occurrences (all)                  | 28               | 11               | 21               |
| NEUTROPHIL COUNT DECREASED         |                  |                  |                  |
| subjects affected / exposed        | 4 / 83 (4.82%)   | 2 / 41 (4.88%)   | 6 / 79 (7.59%)   |
| occurrences (all)                  | 4                | 2                | 13               |
| NEUTROPHIL COUNT INCREASED         |                  |                  |                  |
| subjects affected / exposed        | 35 / 83 (42.17%) | 20 / 41 (48.78%) | 35 / 79 (44.30%) |
| occurrences (all)                  | 65               | 44               | 80               |
| PLATELET COUNT DECREASED           |                  |                  |                  |
| subjects affected / exposed        | 3 / 83 (3.61%)   | 3 / 41 (7.32%)   | 6 / 79 (7.59%)   |
| occurrences (all)                  | 3                | 5                | 8                |
| PLATELET COUNT INCREASED           |                  |                  |                  |
| subjects affected / exposed        | 9 / 83 (10.84%)  | 3 / 41 (7.32%)   | 3 / 79 (3.80%)   |
| occurrences (all)                  | 11               | 5                | 5                |
| RED BLOOD CELL COUNT<br>INCREASED  |                  |                  |                  |
| subjects affected / exposed        | 15 / 83 (18.07%) | 9 / 41 (21.95%)  | 16 / 79 (20.25%) |
| occurrences (all)                  | 30               | 18               | 29               |
| PROTHROMBIN TIME PROLONGED         |                  |                  |                  |

|                                                                                                                                 |                         |                        |                         |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                                                                | 4 / 83 (4.82%)<br>14    | 1 / 41 (2.44%)<br>4    | 5 / 79 (6.33%)<br>9     |
| WHITE BLOOD CELL COUNT<br>DECREASED<br>subjects affected / exposed<br>occurrences (all)                                         | 25 / 83 (30.12%)<br>46  | 10 / 41 (24.39%)<br>15 | 25 / 79 (31.65%)<br>51  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)                                        | 44 / 83 (53.01%)<br>97  | 17 / 41 (41.46%)<br>36 | 42 / 79 (53.16%)<br>82  |
| General disorders and administration<br>site conditions<br>CHILLS<br>subjects affected / exposed<br>occurrences (all)           | 22 / 83 (26.51%)<br>32  | 6 / 41 (14.63%)<br>14  | 20 / 79 (25.32%)<br>36  |
| FATIGUE<br>subjects affected / exposed<br>occurrences (all)                                                                     | 42 / 83 (50.60%)<br>100 | 17 / 41 (41.46%)<br>39 | 42 / 79 (53.16%)<br>88  |
| INJECTION SITE ERYTHEMA<br>subjects affected / exposed<br>occurrences (all)                                                     | 30 / 83 (36.14%)<br>49  | 11 / 41 (26.83%)<br>17 | 49 / 79 (62.03%)<br>83  |
| INJECTION SITE INDURATION<br>subjects affected / exposed<br>occurrences (all)                                                   | 27 / 83 (32.53%)<br>37  | 4 / 41 (9.76%)<br>4    | 39 / 79 (49.37%)<br>72  |
| INJECTION SITE PAIN<br>subjects affected / exposed<br>occurrences (all)                                                         | 78 / 83 (93.98%)<br>197 | 16 / 41 (39.02%)<br>28 | 77 / 79 (97.47%)<br>227 |
| MALAISE<br>subjects affected / exposed<br>occurrences (all)                                                                     | 30 / 83 (36.14%)<br>66  | 12 / 41 (29.27%)<br>23 | 36 / 79 (45.57%)<br>80  |
| Immune system disorders<br>MEAN CELL HAEMOGLOBIN<br>CONCENTRATION DECREASED<br>subjects affected / exposed<br>occurrences (all) | 53 / 83 (63.86%)<br>110 | 28 / 41 (68.29%)<br>61 | 54 / 79 (68.35%)<br>111 |
| Gastrointestinal disorders<br>NAUSEA                                                                                            |                         |                        |                         |

|                                                  |                        |                        |                        |
|--------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 21 / 83 (25.30%)<br>37 | 10 / 41 (24.39%)<br>23 | 23 / 79 (29.11%)<br>40 |
| Musculoskeletal and connective tissue disorders  |                        |                        |                        |
| ARTHRALGIA                                       |                        |                        |                        |
| subjects affected / exposed                      | 24 / 83 (28.92%)       | 6 / 41 (14.63%)        | 23 / 79 (29.11%)       |
| occurrences (all)                                | 34                     | 15                     | 39                     |
| MYALGIA                                          |                        |                        |                        |
| subjects affected / exposed                      | 37 / 83 (44.58%)       | 7 / 41 (17.07%)        | 35 / 79 (44.30%)       |
| occurrences (all)                                | 61                     | 22                     | 64                     |
| Infections and infestations                      |                        |                        |                        |
| SINUSITIS                                        |                        |                        |                        |
| subjects affected / exposed                      | 6 / 83 (7.23%)         | 0 / 41 (0.00%)         | 5 / 79 (6.33%)         |
| occurrences (all)                                | 6                      | 0                      | 5                      |
| UPPER RESPIRATORY TRACT INFECTION                |                        |                        |                        |
| subjects affected / exposed                      | 4 / 83 (4.82%)         | 4 / 41 (9.76%)         | 8 / 79 (10.13%)        |
| occurrences (all)                                | 7                      | 4                      | 12                     |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12 January 2006 | <p>The evaluation of immunogenicity measured as breadth of BCA and ELISA in a subgroup of subjects 7 days after the third dose was added. It was added that a subgroup of 15 consecutive subjects enrolled at sites 01, 03, and 08 were to provide samples for additional clinical laboratory safety testing including coagulation tests according to the Time and Events Table. This subgroup was to have extended chemistry laboratory evaluations performed at baseline and 7 days after each injection and provide serology samples 7 days after the third injection. The clinical lab safety tests should include PT, INR, PTT, fibrinogen and D-dimer coagulation tests.</p> <p>To provide stopping rules pertaining to clinical laboratory evaluations the following sentence was added: "In the event that any clinical laboratory value is in the alert range and is thought to be related to study vaccine, the study will temporarily be halted."</p> <p>To exclude a medication known to affect liver function testing the following exclusion criterion was added: "are currently receiving or have received Accutane (Isotretinoin) in the previous 14 days".</p> <p>The amount of NaCl in the rMenB + OMV vaccine was corrected to 3 mg per 0.5 mL dose.</p> <p>It was clarified that abnormal clinical lab results were not to be graded as mild, moderate or severe.</p> <p>The criteria for assessing safety objectives were inadvertently not included in the original protocol and were therefore added in the amendment</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported