



## Clinical trial results:

### A Phase 3b, Randomized, Open-Label, Multi-Center Study to Evaluate the Safety and Immunogenicity of 2 or 3 Doses of MenACWY Conjugate Vaccine in Healthy Infants and the Effects of a Booster Dose of MenACWY Administered in the Second Year of Life.

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

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-004577-16 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 10 May 2012    |

## Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 01 June 2016  |
| First version publication date | 07 January 2015   |
| Version creation reason        | <ul style="list-style-type: none"><li>Correction of full data set re-QC study because of EudraCT system glitch and updates to results are required including shifting of CI values.</li></ul> |

## Trial information

### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | V59_36 |
|-----------------------|--------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01214837 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Vaccines and Diagnostics  |
| Sponsor organisation address | 350 Massachusetts Avenue, Cambridge, United States, 02139                      |
| 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                       | 01 August 2014 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 10 May 2012    |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To assess the immunogenicity of a 3-dose vaccination schedule of MenACWY vaccine (2 infant doses at 2 and 4 months of age followed by a toddler dose at 12 months of age) compared to a 4-dose vaccination schedule (3 infant doses at 2, 4 and 6 months of age followed by a toddler dose at 12 months of age). The study also characterized immune responses following the first, second and third infant doses, and evaluated the effect of concomitant administration of MenACWY and PCV-13 on immune responses to PCV-13 antigens.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 11 October 2010 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 86         |
| Country: Number of subjects enrolled | United States: 665 |
| Worldwide total number of subjects   | 751                |
| 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) | 751 |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 0   |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 751 subjects were enrolled in this study, with 127 and 129 subjects following a 4-dose vaccination schedule of MenACWY (ACWY4a and ACWY4b groups, respectively), 249 subjects following a 3-dose vaccination schedule (ACWY3 group), and 246 subjects received routine vaccinations alone

### Pre-assignment

Screening details:

All enrolled subjects were included in the study.

### Period 1

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

Blinding implementation details:

Laboratory staff was blinded to the study group allocation when processing serological samples.

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | MenACWY3 |

Arm description:

Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Novartis meningococcal ACWY conjugate vaccine (MenACWY-CRM197, Menveo™) and Routine Vaccines, PCV 13 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solution for solution for injection   |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

0.5mL of dose was administered intra muscularly

|                  |          |
|------------------|----------|
| <b>Arm title</b> | MenACWY4 |
|------------------|----------|

Arm description:

Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Novartis meningococcal ACWY conjugate vaccine (MenACWY-CRM197, Menveo™) and Routine Vaccines, PCV 13 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder and solution for solution for injection   |
| Routes of administration               | Intramuscular use  |

Dosage and administration details:

0.5mL of dose was administered intra muscularly

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Routine vaccines |
|------------------|------------------|

Arm description:

Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.

|          |                  |
|----------|------------------|
| Arm type | Routine Vaccines |
|----------|------------------|

|  |                          |
|--|--------------------------|
| Investigational medicinal product name | Routine Vaccines, PCV 13 |
| Investigational medicinal product code |                          |
| Other name                             |                          |
| Pharmaceutical forms                   | Suspension for injection |
| Routes of administration               | Intramuscular use        |

Dosage and administration details:

Routine infant vaccines were to be administered to subjects according routine methods and schedules for the region.

| <b>Number of subjects in period 1</b> | MenACWY3 | MenACWY4 | Routine vaccines |
|---------------------------------------|----------|----------|------------------|
| Started                               | 249      | 256      | 246              |
| Completed                             | 195      | 192      | 184              |
| Not completed                         | 54       | 64       | 62               |
| Adverse event, non-fatal              | 1        | 2        | 1                |
| Death                                 | -        | -        | 1                |
| Administrative Reason                 | 2        | 6        | 4                |
| Withdrawal by Subject                 | 27       | 36       | 28               |
| Inappropriate enrolment               | -        | 1        | 2                |
| Lost to follow-up                     | 20       | 15       | 21               |
| Unable to Classify                    | 1        | 3        | -                |
| Protocol deviation                    | 3        | 1        | 5                |

## Baseline characteristics

### Reporting groups

|   |                  |
|---|------------------|
| Reporting group title   | MenACWY3         |
| Reporting group description:  |                  |
| Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.  |                  |
| Reporting group title   | MenACWY4         |
| Reporting group description:  |                  |
| Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4. |                  |
| Reporting group title   | Routine vaccines |
| Reporting group description:  |                  |
| Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.  |                  |

| Reporting group values                             | MenACWY3 | MenACWY4 | Routine vaccines |
|--|----------|----------|------------------|
| Number of subjects                                 | 249      | 256      | 246              |
| Age categorical                                    |          |          |                  |
| Units: Subjects                                    |          |          |                  |
| In utero   | 0        | 0        | 0                |
| Preterm newborn infants (gestational age < 37 wks) | 0        | 0        | 0                |
| Newborns (0-27 days)                               | 0        | 0        | 0                |
| Infants and toddlers (28 days-23 months)           | 249      | 256      | 246              |
| Children (2-11 years)                              | 0        | 0        | 0                |
| Adolescents (12-17 years)                          | 0        | 0        | 0                |
| Adults (18-64 years)                               | 0        | 0        | 0                |
| From 65-84 years                                   | 0        | 0        | 0                |
| 85 years and over                                  | 0        | 0        | 0                |
| Age continuous                                     |          |          |                  |
| Units: days  |          |          |                  |
| arithmetic mean                                    | 66.4     | 66.7     | 66.7             |
| standard deviation                                 | ± 7.1    | ± 7.4    | ± 7              |
| Gender categorical                                 |          |          |                  |
| Units: Subjects                                    |          |          |                  |
| Female   | 126      | 123      | 106              |
| Male   | 123      | 133      | 140              |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 751   |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                               | 0     |  |  |
| Infants and toddlers (28 days-23 months)           | 751   |  |  |

|  |     |  |  |
|--|-----|--|--|
| Children (2-11 years)  | 0   |  |  |
| Adolescents (12-17 years)  | 0   |  |  |
| Adults (18-64 years)   | 0   |  |  |
| From 65-84 years   | 0   |  |  |
| 85 years and over  | 0   |  |  |
| Age continuous<br>Units: days<br>arithmetic mean<br>standard deviation | -   |  |  |
| Gender categorical<br>Units: Subjects                                  |     |  |  |
| Female   | 355 |  |  |
| Male   | 396 |  |  |

## End points

### End points reporting groups

|   |                        |
|---|------------------------|
| Reporting group title   | MenACWY3               |
| Reporting group description:<br>Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.  |                        |
| Reporting group title   | MenACWY4               |
| Reporting group description:<br>Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4. |                        |
| Reporting group title   | Routine vaccines       |
| Reporting group description:<br>Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.  |                        |
| Subject analysis set title  | All Enrolled Set       |
| Subject analysis set type   | Intention-to-treat     |
| Subject analysis set description:<br>All subjects who had signed an informed consent, undergone screening procedure and were randomized.  |                        |
| Subject analysis set title  | Toddler PCV PPS        |
| Subject analysis set type   | Per protocol           |
| Subject analysis set description:<br>All subjects who received doses of ACWY and PCV vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding through 13 month timepoint.  |                        |
| Subject analysis set title  | Toddler ACWY PPS       |
| Subject analysis set type   | Per protocol           |
| Subject analysis set description:<br>All subjects who received doses of ACWY vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding through 13 month timepoint.  |                        |
| Subject analysis set title  | Solicited Safety Set   |
| Subject analysis set type   | Safety analysis        |
| Subject analysis set description:<br>All subjects in the Exposed Set with solicited adverse event data  |                        |
| Subject analysis set title  | Unsolicited Safety Set |
| Subject analysis set type   | Safety analysis        |
| Subject analysis set description:<br>All subjects in the Exposed Set with unsolicited adverse event data.   |                        |
| Subject analysis set title  | Infant ACWY PPS        |
| Subject analysis set type   | Per protocol           |
| Subject analysis set description:<br>All subjects who received doses of ACWY vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding, through the 7 month timepoint.  |                        |
| Subject analysis set title  | Infant PCV PPS         |
| Subject analysis set type   | Per protocol           |
| Subject analysis set description:<br>All subjects who received doses of ACWY and PCV vaccine correctly, and provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding, through the 7 month timepoint.  |                        |



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**Primary: 1. Percentage of subjects with serum bactericidal activity using human complement (hSBA)  $\geq$ 1:8, directed against N meningitidis serogroups A, C, W and Y.**

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|                 |  |
|-----------------|--|
| End point title | 1. Percentage of subjects with serum bactericidal activity using human complement (hSBA) $\geq$ 1:8, directed against N meningitidis serogroups A, C, W and Y. <sup>[1][2]</sup> |
|-----------------|--|

**End point description:**

The immune response was assessed in terms of percentage of subjects with hSBA  $\geq$  1:8 against N. meningitidis serogroups A, C, W and Y following 4 doses of Men ACWY vaccine given to infants at 2, 4, 6 and 12 months of age.

Analysis was done on the Toddler Per Protocol Population

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

**End point timeframe:**

13 months of age

**Notes:**

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

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

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | MenACWY4        |  |  |  |
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 152             |  |  |  |
| Units: Percentages of Subjects   |                 |  |  |  |
| number (confidence interval 95%) |                 |  |  |  |
| Serogroup A (N=141)              | 96 (91 to 98)   |  |  |  |
| Serogroup C                      | 99 (95 to 100)  |  |  |  |
| Serogroup W (N=138)              | 99 (96 to 100)  |  |  |  |
| Serogroup Y (N=146)              | 99 (96 to 100)  |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: 2. Percentage of Subjects With hSBA  $\geq$  1:8 Against N Meningitidis Serogroups A, C, W and Y Following 4- Dose and 3-Dose Schedule of Men ACWY Vaccination.**

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|                 |  |
|-----------------|--|
| End point title | 2. Percentage of Subjects With hSBA $\geq$ 1:8 Against N Meningitidis Serogroups A, C, W and Y Following 4- Dose and 3-Dose Schedule of Men ACWY Vaccination. <sup>[3]</sup> |
|-----------------|--|

**End point description:**

The immune response was assessed in terms of percentage of subjects with hSBA  $\geq$  1:8 against N meningitidis serogroups A, C, W and Y following 4 doses of Men ACWY vaccine given to infants at 2, 4, 6 and 12 months of age and 3 doses of Men ACWY given to infants at 2, 4 and 12 months of age.

Analysis was done on Toddler ACWY PPS.

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

**End point timeframe:**

13 months of age

**Notes:**

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

| End point values                 | MenACWY3        | MenACWY4        |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 160             | 152             |  |  |
| Units: Percentages of Subjects   |                 |                 |  |  |
| number (confidence interval 95%) |                 |                 |  |  |
| Serogroup A (N=146, 141)         | 88 (82 to 93)   | 96 (91 to 98)   |  |  |
| Serogroup C                      | 95 (90 to 98)   | 99 (95 to 100)  |  |  |
| Serogroup W (N=153, 138)         | 99 (96 to 100)  | 99 (96 to 100)  |  |  |
| Serogroup Y (N=154, 146)         | 100 (98 to 100) | 99 (96 to 100)  |  |  |

## Statistical analyses

| Statistical analysis title  | Percentage of Subjects With hSBA $\geq$ 1:8 |
|---|---|
| Statistical analysis description:   |   |
| Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup A at 13 months of age. |   |
| Comparison groups   | MenACWY4 v MenACWY3                         |
| Number of subjects included in analysis   | 312   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | non-inferiority <sup>[4]</sup>              |
| Method  | Miettinen and Nurminen method               |
| Parameter estimate  | Group difference                            |
| Point estimate  | -7  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | -14   |
| upper limit   | -1  |

Notes:

[4] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers  $\geq$  1:8 against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

| Statistical analysis title  | Percentage of Subjects With hSBA $\geq$ 1:8 |
|---|---|
| Statistical analysis description:   |   |
| Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup C at 13 months of age. |   |
| Comparison groups   | MenACWY3 v MenACWY4                         |
| Number of subjects included in analysis   | 312   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | non-inferiority <sup>[5]</sup>              |
| Method  | Miettinen and Nurminen method               |
| Parameter estimate  | Risk difference (RD)                        |
| Point estimate  | -4  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -8      |
| upper limit         | 0       |

Notes:

[5] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Percentage of Subjects With hSBA $\geq 1:8$ |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup W at 13 months of age.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | MenACWY3 v MenACWY4            |
| Number of subjects included in analysis | 312                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[6]</sup> |
| Method                                  | Miettinen and Nurminen method  |
| Parameter estimate                      | Risk difference (RD)           |
| Point estimate                          | 0                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -3                             |
| upper limit                             | 3                              |

Notes:

[6] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Percentage of Subjects With hSBA $\geq 1:8$ |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority of Men ACWY 3-dose series (doses at 2, 4 and 12 months) to 4-dose series (doses at 2, 4, 6 and 12 months of age) against serogroup Y at 13 months of age.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | MenACWY3 v MenACWY4            |
| Number of subjects included in analysis | 312                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[7]</sup> |
| Method                                  | Miettinen and Nurminen method  |
| Parameter estimate                      | Risk difference (RD)           |
| Point estimate                          | 1                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2                             |
| upper limit                             | 4                              |

Notes:

[7] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the difference in percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups C, W and Y between the 3-dose series and (minus) the 4-dose series, is greater than -10%.

**Secondary: 3. Percentage of Subjects With hSBA  $\geq 1:8$  Against N. Meningitidis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.**

|                 |  |
|-----------------|--|
| End point title | 3. Percentage of Subjects With hSBA $\geq 1:8$ Against N. Meningitidis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age. |
|-----------------|--|

End point description:

Antibody levels were assessed in terms of percentage of subjects with hSBA  $\geq 1:8$  against N. meningitidis serogroups A, C, W and Y at baseline (2 months of age) and at 3, 4, 5 and 7 months of age.

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

End point timeframe:

Baseline (2 months of age), 3 months, 4 months , 5 months and 7 months of age

| End point values                      | MenACWY3        | MenACWY4        | Routine vaccines |  |
|---------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                    | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed           | 185             | 176             | 187              |  |
| Units: Percentages of Subjects        |                 |                 |                  |  |
| number (confidence interval 95%)      |                 |                 |                  |  |
| Serogroup A (baseline; N=0,0,166)     | 0 (0 to 0)      | 0 (0 to 0)      | 4 (1 to 8)       |  |
| Serogroup A (3 months; N=0,82,0)      | 0 (0 to 0)      | 9 (4 to 17)     | 0 (0 to 0)       |  |
| Serogroup A (4 months; N=0,70,0)      | 0 (0 to 0)      | 4 (1 to 12)     | 0 (0 to 0)       |  |
| Serogroup A (5 months; N=157,0,0)     | 43 (35 to 51)   | 0 (0 to 0)      | 0 (0 to 0)       |  |
| Serogroup A (7 months; N=169,157,171) | 23 (17 to 30)   | 84 (77 to 89)   | 1 (0.015 to 3)   |  |
| Serogroup C (baseline; N=0,0,167)     | 0 (0 to 0)      | 0 (0 to 0)      | 9 (5 to 14)      |  |
| Serogroup C (3 months; N=0,85,0)      | 0 (0 to 0)      | 28 (19 to 39)   | 0 (0 to 0)       |  |
| Serogroup C (4 months; N=0,70,0)      | 0 (0 to 0)      | 41 (30 to 54)   | 0 (0 to 0)       |  |
| Serogroup C (5 months; N=170,0,0)     | 86 (80 to 91)   | 0 (0 to 0)      | 0 (0 to 0)       |  |
| Serogroup C (7 months)                | 71 (64 to 78)   | 95 (91 to 98)   | 1 (0.014 to 3)   |  |
| Serogroup W (baseline; N=0,0,157)     | 0 (0 to 0)      | 0 (0 to 0)      | 20 (14 to 28)    |  |
| Serogroup W (3 months; N=0,84,0)      | 0 (0 to 0)      | 15 (9 to 25)    | 0 (0 to 0)       |  |
| Serogroup W (4 months; N=0,71,0)      | 0 (0 to 0)      | 35 (24 to 47)   | 0 (0 to 0)       |  |
| Serogroup W (5 months; N=162,0,0)     | 86 (80 to 91)   | 0 (0 to 0)      | 0 (0 to 0)       |  |
| Serogroup W (7 months; N=179,162,181) | 74 (67 to 81)   | 99 (96 to 100)  | 1 (0.014 to 3)   |  |
| Serogroup Y (baseline; N=0,0,150)     | 0 (0 to 0)      | 0 (0 to 0)      | 7 (4 to 13)      |  |
| Serogroup Y (3 months; N=0,80,0)      | 0 (0 to 0)      | 8 (3 to 16)     | 0 (0 to 0)       |  |
| Serogroup Y (4 months; N=0,69,0)      | 0 (0 to 0)      | 7 (2 to 16)     | 0 (0 to 0)       |  |
| Serogroup Y (5 months; N=152,0,0)     | 67 (59 to 75)   | 0 (0 to 0)      | 0 (0 to 0)       |  |
| Serogroup Y (7 months; N=170,163,173) | 48 (40 to 55)   | 94 (90 to 97)   | 0 (0 to 2)       |  |

**Statistical analyses**

**Secondary: 4. Geometric Mean hSBA Titers Against N Meningitis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age.**

|                 |  |
|-----------------|--|
| End point title | 4. Geometric Mean hSBA Titers Against N Meningitis Serogroups A, C, W and Y at Baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age. |
|-----------------|--|

## End point description:

Antibody levels were assessed in terms of geometric mean titers (GMTs) against N. meningitidis serogroups A, C, W and Y at baseline (2 Months of Age) and at 3, 4, 5, and 7 Months of Age. Analysis was done on the Infant ACWY PPS.

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

## End point timeframe:

Baseline (2 months of age), 3 months, 4 months , 5 months and 7 months of age

| End point values                         | MenACWY3            | MenACWY4            | Routine vaccines    |  |
|--|---------------------|---------------------|---------------------|--|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed              | 185                 | 176                 | 187                 |  |
| Units: Titers                            |                     |                     |                     |  |
| geometric mean (confidence interval 95%) |                     |                     |                     |  |
| Serogroup A (baseline; N=0,0,166)        | 0 (0 to 0)          | 0 (0 to 0)          | 2.18 (2.05 to 2.33) |  |
| Serogroup A (3 months; N=0,82,0)         | 0 (0 to 0)          | 2.63 (2.2 to 3.15)  | 0 (0 to 0)          |  |
| Serogroup A (4 months; N=0,70,0)         | 0 (0 to 0)          | 2.18 (2 to 2.37)    | 0 (0 to 0)          |  |
| Serogroup A (5 months; N=157,0,0)        | 7.09 (5.62 to 8.94) | 0 (0 to 0)          | 0 (0 to 0)          |  |
| Serogroup A (7 months; N=169,157,171)    | 3.68 (3.17 to 4.29) | 28 (23 to 35)       | 2.02 (1.98 to 2.06) |  |
| Serogroup C (baseline; N=0,0,167)        | 0 (0 to 0)          | 0 (0 to 0)          | 2.52 (2.28 to 2.78) |  |
| Serogroup C (3 months; N=0,85,0)         | 0 (0 to 0)          | 4.79 (3.71 to 6.19) | 0 (0 to 0)          |  |
| Serogroup C (4 months; N=0,70,0)         | 0 (0 to 0)          | 6.44 (4.83 to 8.59) | 0 (0 to 0)          |  |
| Serogroup C (5 months; N=170,0,0)        | 50 (39 to 64)       | 0 (0 to 0)          | 0 (0 to 0)          |  |
| Serogroup C (7 months)                   | 17 (14 to 22)       | 86 (70 to 104)      | 2.03 (1.97 to 2.08) |  |
| Serogroup W (baseline; N=0,0,157)        | 0 (0 to 0)          | 0 (0 to 0)          | 3.32 (2.82 to 3.9)  |  |
| Serogroup W (3 months; N=0,84,0)         | 0 (0 to 0)          | 3 (2.48 to 3.61)    | 0 (0 to 0)          |  |
| Serogroup W (4 months; N=0,71,0)         | 0 (0 to 0)          | 4.38 (3.42 to 5.61) | 0 (0 to 0)          |  |
| Serogroup W (5 months; N=162,0,0)        | 55 (42 to 71)       | 0 (0 to 0)          | 0 (0 to 0)          |  |
| Serogroup W (7 months; N=179,162,181)    | 17 (14 to 21)       | 90 (77 to 104)      | 2.04 (1.96 to 2.11) |  |
| Serogroup Y (baseline; N=0,0,150)        | 0 (0 to 0)          | 0 (0 to 0)          | 2.47 (2.25 to 2.7)  |  |
| Serogroup Y (3 months; N=0,80,0)         | 0 (0 to 0)          | 2.5 (2.14 to 2.93)  | 0 (0 to 0)          |  |
| Serogroup Y (4 months; N=0,69,0)         | 0 (0 to 0)          | 2.46 (2.16 to 2.79) | 0 (0 to 0)          |  |

|                                       |                     |               |            |  |
|---------------------------------------|---------------------|---------------|------------|--|
| Serogroup Y (5 months; N=152,0,0)     | 20 (15 to 26)       | 0 (0 to 0)    | 0 (0 to 0) |  |
| Serogroup Y (7 months; N=170,163,173) | 7.56 (6.29 to 9.08) | 52 (43 to 64) | 2 (2 to 2) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 5. Percentage of Subjects With hSBA $\geq 1:8$ Following 2 and 3 Infant Doses of MenACWY.

|                 |  |
|-----------------|--|
| End point title | 5. Percentage of Subjects With hSBA $\geq 1:8$ Following 2 and 3 Infant Doses of MenACWY. <sup>[8]</sup> |
|-----------------|--|

End point description:

Percentage of subjects with hSBA  $\geq 1:8$  against N meningitis serogroups A, C, W and Y was assessed following 2 and 3 infant doses of MenACWY as measured prior to the toddler dose at 12 months of age.

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

End point timeframe:

Percentage of Subjects With hSBA  $\geq 1:8$  Following 2 and 3 Infant Doses of MenACWY.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

| End point values                 | MenACWY3        | MenACWY4        |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 149             | 147             |  |  |
| Units: Percentages of Subjects   |                 |                 |  |  |
| number (confidence interval 95%) |                 |                 |  |  |
| Serogroup A (N=141,138)          | 6 (2 to 11)     | 22 (15 to 30)   |  |  |
| Serogroup C                      | 19 (13 to 27)   | 48 (39 to 56)   |  |  |
| Serogroup W (N=149,142)          | 33 (25 to 41)   | 66 (58 to 74)   |  |  |
| Serogroup Y (N=145,139)          | 25 (18 to 33)   | 55 (47 to 64)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 6. Geometric Mean hSBA Titers Following 2 and 3 Infant Doses of MenACWY

|                 |  |
|-----------------|--|
| End point title | 6. Geometric Mean hSBA Titers Following 2 and 3 Infant Doses of MenACWY <sup>[9]</sup> |
|-----------------|--|

End point description:

The immune response was assessed in terms of GMTs against N. meningitidis serogroups A, C, W and Y following 2 and 3 infant doses of MenACWY as measured prior to the toddler dose at 12 months of age.

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

End point timeframe:

12 months of age.

Notes:

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

| End point values                         | MenACWY3            | MenACWY4            |  |  |
|--|---------------------|---------------------|--|--|
| Subject group type                       | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed              | 149                 | 147                 |  |  |
| Units: Titers                            |                     |                     |  |  |
| geometric mean (confidence interval 95%) |                     |                     |  |  |
| Serogroup A (N=141,138)                  | 2.28 (2.09 to 2.49) | 3.65 (3.08 to 4.33) |  |  |
| Serogroup C                              | 3.54 (2.99 to 4.17) | 8.55 (6.75 to 11)   |  |  |
| Serogroup W (N=149,142)                  | 5.41 (4.39 to 6.67) | 13 (11 to 16)       |  |  |
| Serogroup Y (N=145,139)                  | 3.82 (3.24 to 4.49) | 9.65 (7.79 to 12)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: 7. GMTs at 13 Months of Age After Completion of 3- and 4-Dose Series of MenACWY.

|                        |   |
|------------------------|---|
| End point title        | 7. GMTs at 13 Months of Age After Completion of 3- and 4-Dose Series of MenACWY. <sup>[10]</sup>  |
| End point description: | Immune response was assessed in terms of GMTs against N meningitis serogroups A, C, W and Y at 1 month after completion of a 3- and 4- dose series of MenACWY. Analysis was done on the Toddler ACWY PPS. |
| End point type         | Secondary   |
| End point timeframe:   | 13 months of age  |

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

| End point values                         | MenACWY3         | MenACWY4         |  |  |
|--|------------------|------------------|--|--|
| Subject group type                       | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed              | 160              | 152              |  |  |
| Units: Titers                            |                  |                  |  |  |
| geometric mean (confidence interval 95%) |                  |                  |  |  |
| Serogroup A (N=146,141)                  | 59 (45 to 77)    | 94 (76 to 117)   |  |  |
| Serogroup C                              | 124 (99 to 156)  | 160 (130 to 198) |  |  |
| Serogroup W (N=153,138)                  | 248 (202 to 303) | 244 (195 to 305) |  |  |
| Serogroup Y (N=154,146)                  | 212 (175 to 258) | 254 (203 to 318) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 8. Percentage of Subjects With 4-fold Increase in hSBA Titers Against N Meningitis Serogroups A, C, W and Y Between 12 and 13 Months of Age.

|                 |  |
|-----------------|--|
| End point title | 8. Percentage of Subjects With 4-fold Increase in hSBA Titers Against N Meningitis Serogroups A, C, W and Y Between 12 and 13 Months of Age. <sup>[11]</sup> |
|-----------------|--|

#### End point description:

The immune response was assessed in terms of percentage of subjects with 4-fold increase in hSBA titers between post and pre toddler dose against N meningitis serogroups A, C, W and Y, 1 month after completing a 3- or 4-dose series of MenACWY.

Analysis was done on the Toddler PPS.

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

#### End point timeframe:

13 months of age

#### Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

| End point values                 | MenACWY3        | MenACWY4        |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 147             | 147             |  |  |
| Units: Percentages of Subjects   |                 |                 |  |  |
| number (confidence interval 95%) |                 |                 |  |  |
| Serogroup A (N=127,129)          | 88 (81 to 93)   | 95 (90 to 98)   |  |  |
| Serogroup C                      | 93 (88 to 97)   | 91 (85 to 95)   |  |  |
| Serogroup W (N=140,131)          | 98 (94 to 100)  | 90 (84 to 95)   |  |  |
| Serogroup Y (N=139,136)          | 100 (97 to 100) | 96 (91 to 98)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 9. Effect of Concomitant Administration of 3 or 4 Doses of MenACWY on Immune Response to PCV-13 Antigens at 13 Months of Age.

|                 |   |
|-----------------|---|
| End point title | 9. Effect of Concomitant Administration of 3 or 4 Doses of MenACWY on Immune Response to PCV-13 Antigens at 13 Months of Age. |
|-----------------|---|

#### End point description:

Geometric mean concentrations (GMCs) of antibodies against PCV-13 vaccine antigens at 13 months of age following concomitant administration of a 3- or 4-dose series of MenACWY with PCV-13.



Analysis was done on the Toddler PCV PPS.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 13 months of age.    |           |

| End point values                         | MenACWY3            | MenACWY4            | Routine vaccines    |  |
|--|---------------------|---------------------|---------------------|--|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed              | 147                 | 117                 | 124                 |  |
| Units: µg/mL                             |                     |                     |                     |  |
| geometric mean (confidence interval 95%) |                     |                     |                     |  |
| 1 (N=145,116,123)                        | 2 (1.7 to 2.36)     | 2.16 (1.83 to 2.56) | 2.14 (1.8 to 2.54)  |  |
| 3 (N=139,113,118)                        | 0.88 (0.74 to 1.05) | 0.97 (0.81 to 1.15) | 0.77 (0.64 to 0.93) |  |
| 4 (N=146,117,123)                        | 1.19 (0.99 to 1.42) | 1.45 (1.21 to 1.75) | 1.53 (1.27 to 1.86) |  |
| 5 (N=140,114,117)                        | 1.29 (1.11 to 1.49) | 1.35 (1.16 to 1.57) | 1.26 (1.08 to 1.48) |  |
| 6A (N=146,117,124)                       | 6.89 (5.78 to 8.21) | 9.01 (7.52 to 11)   | 8.16 (6.77 to 9.82) |  |
| 6B (N=147,117,124)                       | 4.29 (3.6 to 5.11)  | 5.23 (4.36 to 6.27) | 5.04 (4.18 to 6.08) |  |
| 7F (N=147,116,123)                       | 3.96 (3.42 to 4.58) | 5.14 (4.41 to 5.98) | 4.95 (4.23 to 5.78) |  |
| 9V (N=146,117,123)                       | 1.37 (1.17 to 1.61) | 1.85 (1.56 to 2.18) | 1.73 (1.46 to 2.05) |  |
| 14 (N=147,117,124)                       | 7.76 (6.51 to 9.26) | 7.86 (6.55 to 9.43) | 7.54 (6.25 to 9.09) |  |
| 18C (N=146,116,123)                      | 1.52 (1.28 to 1.8)  | 2.34 (1.96 to 2.79) | 2.13 (1.78 to 2.55) |  |
| 19A (N=144,114,124)                      | 5.51 (4.61 to 6.6)  | 5.23 (4.34 to 6.3)  | 5.39 (4.45 to 6.51) |  |
| 19F (N=147,117,124)                      | 5.79 (4.9 to 6.85)  | 6.19 (5.21 to 7.35) | 5.8 (4.86 to 6.92)  |  |
| 23F (N=147,117,124)                      | 4.21 (3.49 to 5.09) | 4.84 (3.98 to 5.89) | 5.44 (4.45 to 6.65) |  |

## Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | MenACWY3 vs Routine Vaccines (Serotype 1) |
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 1. |   |
| Comparison groups  | MenACWY3 v Routine vaccines               |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[12]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.94                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.77                            |
| upper limit                             | 1.13                            |

Notes:

[12] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (Serotype 1) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 1.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[13]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.02                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.83                            |
| upper limit                             | 1.25                            |

Notes:

[13] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (Serotype 3) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 3.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[14]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.14                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.93                            |
| upper limit                             | 1.4                             |

Notes:

[14] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY4 vs Routine Vaccines (Serotype 3) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 3. |   |
| Comparison groups   | Routine vaccines v MenACWY4               |
| Number of subjects included in analysis   | 241                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | non-inferiority <sup>[15]</sup>           |
| Method  | ANOVA                                     |
| Parameter estimate  | GMC ratio                                 |
| Point estimate  | 1.25                                      |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 1.01                                      |
| upper limit   | 1.55                                      |

Notes:

[15] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY3 vs Routine Vaccines (Serotype 4) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 4. |   |
| Comparison groups   | MenACWY3 v Routine vaccines               |
| Number of subjects included in analysis   | 271                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | non-inferiority <sup>[16]</sup>           |
| Method  | ANOVA                                     |
| Parameter estimate  | GMC ratio                                 |
| Point estimate  | 0.77                                      |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 0.62                                      |
| upper limit   | 0.96                                      |

Notes:

[16] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY4 vs Routine Vaccines (serotype 4) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 4. |   |
| Comparison groups   | Routine vaccines v MenACWY4               |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[17]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.94                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.75                            |
| upper limit                             | 1.18                            |

Notes:

[17] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (Serotype 5) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 5.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[18]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.02                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.86                            |
| upper limit                             | 1.21                            |

Notes:

[18] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (Serotype 5) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 5.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[19]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.07                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.89                            |
| upper limit                             | 1.29                            |

Notes:

[19] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5

| Statistical analysis title   | MenACWY3 vs Routine Vaccines (serotype 6A) |
|--|--|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6A. |  |
| Comparison groups  | MenACWY3 v Routine vaccines                |
| Number of subjects included in analysis  | 271  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | non-inferiority <sup>[20]</sup>            |
| Method   | ANOVA                                      |
| Parameter estimate   | GMC ratio                                  |
| Point estimate   | 0.85                                       |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | 0.69                                       |
| upper limit  | 1.04                                       |

Notes:

[20] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title              | MenACWY4 vs Routine Vaccines (serotype 6A) |
|---|--|
| Comparison groups                       | MenACWY4 v Routine vaccines                |
| Number of subjects included in analysis | 241  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | non-inferiority <sup>[21]</sup>            |
| Method                                  | ANOVA                                      |
| Parameter estimate                      | GMC ratio                                  |
| Point estimate                          | 1.1  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 0.88                                       |
| upper limit                             | 1.37                                       |

Notes:

[21] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

| Statistical analysis title   | MenACWY3 vs Routine Vaccines (serotype 6B) |
|--|--|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6B. |  |
| Comparison groups  | MenACWY3 v Routine vaccines                |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[22]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.85                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.69                            |
| upper limit                             | 1.05                            |

Notes:

[22] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 6B) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 6B.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[23]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.04                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.83                            |
| upper limit                             | 1.3                             |

Notes:

[23] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (serotype 7F) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 7F.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[24]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.8                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.67                            |
| upper limit                             | 0.95                            |

Notes:

[24] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title   | MenACWY4 vs Routine Vaccines (serotype 7F) |
|--|--|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 7F. |  |
| Comparison groups  | MenACWY4 v Routine vaccines                |
| Number of subjects included in analysis  | 241  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | non-inferiority <sup>[25]</sup>            |
| Method   | ANOVA                                      |
| Parameter estimate   | GMC ratio                                  |
| Point estimate   | 1.04                                       |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | 0.87                                       |
| upper limit  | 1.25                                       |

Notes:

[25] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

| Statistical analysis title   | MenACWY3 vs Routine Vaccines (serotype 9V) |
|--|--|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 9V. |  |
| Comparison groups  | MenACWY3 v Routine vaccines                |
| Number of subjects included in analysis  | 271  |
| Analysis specification   | Pre-specified                              |
| Analysis type  | non-inferiority <sup>[26]</sup>            |
| Method   | ANOVA                                      |
| Parameter estimate   | GMC ratio                                  |
| Point estimate   | 0.79                                       |
| Confidence interval  |  |
| level  | 95 %                                       |
| sides  | 2-sided                                    |
| lower limit  | 0.66                                       |
| upper limit  | 0.96                                       |

Notes:

[26] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title   | MenACWY4 vs Routine Vaccines (serotype 9V) |
|--|--|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 9V. |  |
| Comparison groups  | MenACWY4 v Routine vaccines                |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[27]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.07                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.87                            |
| upper limit                             | 1.31                            |

Notes:

[27] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (serotype 14) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 14.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[28]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.03                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.84                            |
| upper limit                             | 1.27                            |

Notes:

[28] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 14) |
|-----------------------------------|--|

Statistical analysis description:

demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 14.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[29]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.04                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.83                            |
| upper limit                             | 1.3                             |



Notes:

[29] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY3 vs Routine Vaccines (serotype 18C) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 18C. |   |
| Comparison groups   | MenACWY3 v Routine vaccines                 |
| Number of subjects included in analysis   | 271   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | non-inferiority <sup>[30]</sup>             |
| Method  | ANOVA                                       |
| Parameter estimate  | GMC ratio                                   |
| Point estimate  | 0.72  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | 0.59  |
| upper limit   | 0.87  |

Notes:

[30] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY4 vs Routine Vaccines (serotype 18C) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 18C. |   |
| Comparison groups   | MenACWY4 v Routine vaccines                 |
| Number of subjects included in analysis   | 241   |
| Analysis specification  | Pre-specified                               |
| Analysis type   | non-inferiority <sup>[31]</sup>             |
| Method  | ANOVA                                       |
| Parameter estimate  | GMC ratio                                   |
| Point estimate  | 1.1   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided                                     |
| lower limit   | 0.89  |
| upper limit   | 1.36  |

Notes:

[31] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

| Statistical analysis title  | MenACWY3 vs Routine Vaccines (serotype 19A) |
|---|---|
| Statistical analysis description:<br>To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19A. |   |
| Comparison groups   | MenACWY3 v Routine vaccines                 |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[32]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1.02                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.83                            |
| upper limit                             | 1.27                            |

Notes:

[32] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 19A) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19A.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[33]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.97                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.77                            |
| upper limit                             | 1.21                            |

Notes:

[33] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (serotype 19F) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19F.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 271                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[34]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 1                               |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.82                            |
| upper limit                             | 1.22                            |

Notes:

[34] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between groups (MenACWY3 to routine vaccines) is greater than 0.5.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | MenACWY4 vs Routine Vaccines (serotype 19F) |
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 4 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 19F. |   |
| Comparison groups  | MenACWY4 v Routine vaccines                 |
| Number of subjects included in analysis  | 241   |
| Analysis specification   | Pre-specified                               |
| Analysis type  | non-inferiority <sup>[35]</sup>             |
| Method   | ANOVA                                       |
| Parameter estimate   | GMC ratio                                   |
| Point estimate   | 1.07  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                     |
| lower limit  | 0.86  |
| upper limit  | 1.32  |

Notes:

[35] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | MenACWY3 vs Routine Vaccines (serotype 23F) |
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 13 months of age for Serotype 23F. |   |
| Comparison groups  | Routine vaccines v MenACWY3                 |
| Number of subjects included in analysis  | 271   |
| Analysis specification   | Pre-specified                               |
| Analysis type  | non-inferiority <sup>[36]</sup>             |
| Method   | ANOVA                                       |
| Parameter estimate   | GMC ratio                                   |
| Point estimate   | 0.77  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                     |
| lower limit  | 0.62  |
| upper limit  | 0.97  |

Notes:

[36] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY3 to routine vaccines) is greater than 0.5.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 23F) |
| Comparison groups                 | MenACWY4 v Routine vaccines                 |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 241                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[37]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | GMC ratio                       |
| Point estimate                          | 0.89                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.7                             |
| upper limit                             | 1.13                            |

Notes:

[37] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI around the ratio of GMCs between the groups (MenACWY4 to routine vaccines) is greater than 0.5.

### **Secondary: 10. Effect of Concomitant Administration of 2 or 3 Doses of MenACWY on Immune Response to PCV-13 Antigens at 7 Months of Age.**

|                 |   |
|-----------------|---|
| End point title | 10. Effect of Concomitant Administration of 2 or 3 Doses of MenACWY on Immune Response to PCV-13 Antigens at 7 Months of Age. |
|-----------------|---|

End point description:

Percentage of subjects with IgG concentration  $\geq 0.35$  µg/mL against pneumococcal conjugate vaccine (PCV-13) antigens at 7 Months of age following concomitant administration of 2 or 3 doses of MenACWY with PCV-13.

Analysis was done on Infant PCV PPS

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

End point timeframe:

7 months of age.

| <b>End point values</b>          | MenACWY3            | MenACWY4            | Routine vaccines    |  |
|----------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type               | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed      | 160                 | 137                 | 158                 |  |
| Units: Percentages of Subjects   |                     |                     |                     |  |
| number (confidence interval 95%) |                     |                     |                     |  |
| 1 (N=159,136,156)                | 93.7 (88.7 to 96.9) | 100 (97.3 to 100)   | 94.2 (89.3 to 97.3) |  |
| 3 (N=150,129,147)                | 79.3 (72 to 85.5)   | 87.6 (80.6 to 92.7) | 82.3 (75.2 to 88.1) |  |
| 4 (N=160,137,157)                | 94.4 (89.6 to 97.4) | 97.1 (92.7 to 99.2) | 96.8 (92.7 to 99)   |  |
| 5 (N=156,133,154)                | 84 (77.3 to 89.4)   | 93.2 (87.5 to 96.9) | 88.3 (82.2 to 92.9) |  |
| 6A (N=159,136,156)               | 98.1 (94.6 to 99.6) | 99.3 (96 to 100)    | 98.1 (94.5 to 99.6) |  |
| 6B (N=160,137,157)               | 84.4 (77.8 to 89.6) | 94.9 (89.8 to 97.9) | 84.7 (78.1 to 90)   |  |
| 7F (N=158,136,156)               | 100 (97.7 to 100)   | 100 (97.3 to 100)   | 99.4 (96.5 to 100)  |  |
| 9V (N=159,136,157)               | 89.3 (83.4 to 93.6) | 96.3 (91.6 to 98.8) | 92.4 (87 to 96)     |  |
| 14 (N=158,136,158)               | 99.4 (96.5 to 100)  | 100 (97.3 to 100)   | 97.5 (93.6 to 99.3) |  |

|                     |                     |                     |                     |  |
|---------------------|---------------------|---------------------|---------------------|--|
| 18C (N=158,136,157) | 97.5 (93.6 to 99.3) | 97.8 (93.7 to 99.5) | 100 (97.7 to 100)   |  |
| 19A (N=158,135,156) | 95.6 (91.1 to 98.2) | 92.6 (86.8 to 96.4) | 98.1 (94.5 to 99.6) |  |
| 19F (N=159,136,158) | 100 (97.7 to 100)   | 100 (97.3 to 100)   | 99.4 (96.5 to 100)  |  |
| 23F (N=158,136,158) | 93 (87.9 to 96.5)   | 95.6 (90.6 to 98.4) | 91.1 (85.6 to 98.4) |  |

## Statistical analyses

| Statistical analysis title   | MenACWY3 vs Routine Vaccines (Serotype 1) |
|--|---|
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 1. |   |
| Comparison groups  | MenACWY3 v Routine vaccines               |
| Number of subjects included in analysis  | 318                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | non-inferiority <sup>[38]</sup>           |
| Method   | Miettinen and Nurminen method             |
| Parameter estimate   | Risk difference (RD)                      |
| Point estimate   | -0.5                                      |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | -6.1                                      |
| upper limit  | 5   |

Notes:

[38] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

| Statistical analysis title  | MenACWY4 vs Routine Vaccines (Serotype 1) |
|---|---|
| Statistical analysis description:   |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 1. |   |
| Comparison groups   | MenACWY4 v Routine vaccines               |
| Number of subjects included in analysis   | 295                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | non-inferiority <sup>[39]</sup>           |
| Method  | Miettinen and Nurminen method             |
| Parameter estimate  | Risk difference (RD)                      |
| Point estimate  | 5.8                                       |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | 3   |
| upper limit   | 10.5                                      |

Notes:

[39] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | MenACWY3 vs Routine Vaccines (Serotype 3) |
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 3. |   |
| Comparison groups  | MenACWY3 v Routine vaccines               |
| Number of subjects included in analysis  | 318                                       |
| Analysis specification   | Pre-specified                             |
| Analysis type  | non-inferiority <sup>[40]</sup>           |
| Method   | Miettinen and Nurminen method             |
| Parameter estimate   | Risk difference (RD)                      |
| Point estimate   | -3  |
| Confidence interval  |   |
| level  | 95 %                                      |
| sides  | 2-sided                                   |
| lower limit  | -11.9                                     |
| upper limit  | 6   |

Notes:

[40] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | MenACWY4 vs Routine Vaccines (serotype 3) |
| Statistical analysis description:   |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 3. |   |
| Comparison groups   | MenACWY4 v Routine vaccines               |
| Number of subjects included in analysis   | 295                                       |
| Analysis specification  | Pre-specified                             |
| Analysis type   | non-inferiority <sup>[41]</sup>           |
| Method  | Miettinen and Nurminen method             |
| Parameter estimate  | Risk difference (RD)                      |
| Point estimate  | 5.3                                       |
| Confidence interval   |   |
| level   | 95 %                                      |
| sides   | 2-sided                                   |
| lower limit   | -3.3                                      |
| upper limit   | 13.7                                      |

Notes:

[41] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | MenACWY3 vs Routine Vaccines (serotype 4) |
| Statistical analysis description:  |   |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 4. |   |
| Comparison groups  | MenACWY3 v Routine vaccines               |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[42]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -2.4                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -7.5                            |
| upper limit                             | 2.3                             |

Notes:

[42] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 4) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 4.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[43]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 0.3                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -4.4                            |
| upper limit                             | 4.7                             |

Notes:

[43] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine Vaccines (serotype 5) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 5.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[44]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -4.3                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -12.1   |
| upper limit         | 3.4     |

Notes:

[44] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine Vaccines (serotype 5) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 5.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[45]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 4.9                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.9                            |
| upper limit                             | 11.8                            |

Notes:

[45] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serogroup 6A) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6A.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[46]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 0.04                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -3.7                            |
| upper limit                             | 3.8                             |

Notes:

[46] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serogroup 6A) |
|-----------------------------------|---|



**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6A.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[47]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 1.2                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -2.2                            |
| upper limit                             | 4.8                             |

**Notes:**

[47] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serogroup 6B) |
|-----------------------------------|---|

**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6B.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[48]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -0.3                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -8.4                            |
| upper limit                             | 7.7                             |

**Notes:**

[48] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serogroup 6B) |
|-----------------------------------|---|

**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 6B.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | MenACWY4 v Routine vaccines |
|-------------------|-----------------------------|

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[49]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 10.2                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 3.4                             |
| upper limit                             | 17.2                            |

Notes:

[49] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 7F) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 7F.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[50]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 0.6                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.7                            |
| upper limit                             | 3.5                             |

Notes:

[50] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serotype 7F) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 7F.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[51]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 0.6                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.1    |
| upper limit         | 3.5     |

Notes:

[51] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 9V) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 9V.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[52]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -3.1                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -9.7                            |
| upper limit                             | 3.4                             |

Notes:

[52] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serotype 9V) |
|-----------------------------------|--|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 9V.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[53]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 4                               |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.5                            |
| upper limit                             | 9.7                             |

Notes:

[53] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 14) |
|-----------------------------------|--|

**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 14.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[54]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 1.9                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.2                            |
| upper limit                             | 5.7                             |

**Notes:**

[54] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serotype 14) |
|-----------------------------------|--|

**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 14.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[55]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 2.5                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -0.2                            |
| upper limit                             | 6.3                             |

**Notes:**

[55] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 18C) |
|-----------------------------------|---|

**Statistical analysis description:**

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 18C.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | MenACWY3 v Routine vaccines |
|-------------------|-----------------------------|

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[56]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -2.5                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -6.3                            |
| upper limit                             | -0.2                            |

Notes:

[56] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35$   $\mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serotype 18C) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 18C.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[57]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -2.2                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -6.2                            |
| upper limit                             | -0.2                            |

Notes:

[57] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35$   $\mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 19A) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19A

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[58]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -2.5                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -7.1    |
| upper limit         | 1.6     |

Notes:

[58] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY4 vs Routine vaccines (serotype 19A) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19A.

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[59]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -5.5                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -11.3                           |
| upper limit                             | -0.9                            |

Notes:

[59] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | MenACWY3 vs Routine vaccines (serotype 19F) |
|-----------------------------------|---|

Statistical analysis description:

To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19F

|   |                                 |
|---|---------------------------------|
| Comparison groups                       | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis | 318                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[60]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 0.6                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.7                            |
| upper limit                             | 3.4                             |

Notes:

[60] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

|  |   |
|--|---|
|  | MenACWY4 vs Routine vaccines (serotype 19F) |
|--|---|

| Statistical analysis title  |                                 |
|---|---------------------------------|
| Statistical analysis description:   |                                 |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 19F. |                                 |
| Comparison groups   | MenACWY4 v Routine vaccines     |
| Number of subjects included in analysis   | 295                             |
| Analysis specification  | Pre-specified                   |
| Analysis type   | non-inferiority <sup>[61]</sup> |
| Method  | Miettinen and Nurminen method   |
| Parameter estimate  | Risk difference (RD)            |
| Point estimate  | 0.6                             |
| Confidence interval   |                                 |
| level   | 95 %                            |
| sides   | 2-sided                         |
| lower limit   | -2.1                            |
| upper limit   | 3.4                             |

Notes:

[61] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

| Statistical analysis title   |                                 |
|--|---------------------------------|
| MenACWY3 vs Routine vaccines (serotype 23F)  |                                 |
| Statistical analysis description:  |                                 |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 2 doses of MenACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 23F. |                                 |
| Comparison groups  | MenACWY3 v Routine vaccines     |
| Number of subjects included in analysis  | 318                             |
| Analysis specification   | Pre-specified                   |
| Analysis type  | non-inferiority <sup>[62]</sup> |
| Method   | Miettinen and Nurminen method   |
| Parameter estimate   | Risk difference (RD)            |
| Point estimate   | 1.9                             |
| Confidence interval  |                                 |
| level  | 95 %                            |
| sides  | 2-sided                         |
| lower limit  | -4.2                            |
| upper limit  | 8.2                             |

Notes:

[62] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY3 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

| Statistical analysis title   |                             |
|--|-----------------------------|
| MenACWY4 vs Routine vaccines (serotype 23F)  |                             |
| Statistical analysis description:  |                             |
| To demonstrate non-inferiority of immune response to PCV-13 antigens after concomitant administration of 3 doses of Men ACWY with routine vaccines including PCV-13, versus administration of routine vaccines only, at 7 months of age for Serotype 23F |                             |
| Comparison groups  | MenACWY4 v Routine vaccines |

|   |                                 |
|---|---------------------------------|
| Number of subjects included in analysis | 295                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[63]</sup> |
| Method                                  | Miettinen and Nurminen method   |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | 4.5                             |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.4                            |
| upper limit                             | 10.5                            |

Notes:

[63] - Non-inferiority will be concluded if the lower limit of the two-sided 95% CI for the between group difference (MenACWY4 minus Routine) in percentage of subjects with IgG concentration  $\geq 0.35 \mu\text{g/mL}$  against each pneumococcal anti-capsular polysaccharide is greater than -10%.

### Secondary: 11. Percentage Of Subjects Reporting at Least One Severe Systemic Solicited Adverse Event

|                 |   |
|-----------------|---|
| End point title | 11. Percentage Of Subjects Reporting at Least One Severe Systemic Solicited Adverse Event |
|-----------------|---|

End point description:

Safety was assessed as the percentage of subjects who reported severe solicited systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

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

End point timeframe:

Day 1 through Day 7

| End point values                          | MenACWY3        | MenACWY4        | Routine vaccines |  |
|---|-----------------|-----------------|------------------|--|
| Subject group type                        | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed               | 238             | 240             | 230              |  |
| Units: Percentage of Subjects             |                 |                 |                  |  |
| number (not applicable)                   |                 |                 |                  |  |
| At least one severe systemic solicited AE | 18              | 21              | 18               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 12. Number Of Subjects Reporting Solicited Local or Systemic Adverse Events after any vaccination.

|                 |  |
|-----------------|--|
| End point title | 12. Number Of Subjects Reporting Solicited Local or Systemic Adverse Events after any vaccination. |
|-----------------|--|

End point description:

Safety was assessed as the number of subjects who reported solicited local or systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone.

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

End point timeframe:

Day 1 (6 hour) to day 7



| End point values                           | MenACWY3        | MenACWY4        | Routine vaccines |  |
|--|-----------------|-----------------|------------------|--|
| Subject group type                         | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed                | 238             | 239             | 229              |  |
| Units: Subjects                            |                 |                 |                  |  |
| number (not applicable)                    |                 |                 |                  |  |
| Injection site erythema                    | 72              | 64              | 79               |  |
| Injection site induration                  | 60              | 40              | 74               |  |
| Tenderness                                 | 117             | 127             | 126              |  |
| Change in eating habits<br>(N=238,238,229) | 104             | 104             | 93               |  |
| Sleepiness                                 | 153             | 147             | 149              |  |
| Persistent crying                          | 140             | 137             | 112              |  |
| Irritability                               | 173             | 171             | 152              |  |
| Vomiting                                   | 68              | 52              | 54               |  |
| Diarrhea                                   | 89              | 69              | 68               |  |
| Fever ( $\geq 38.0^{\circ}\text{C}$ )      | 55              | 52              | 41               |  |
| Rash                                       | 23              | 19              | 18               |  |
| Use of analgesic/antipyretic               | 162             | 173             | 153              |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 13. Number of Subjects Reporting Unsolicited Adverse Events After Any Vaccination

|                        |   |
|------------------------|---|
| End point title        | 13. Number of Subjects Reporting Unsolicited Adverse Events After Any Vaccination   |
| End point description: | Safety was assessed as the number of subjects who reported unsolicited local or systemic adverse events after administration of MenACWY with concomitant vaccines vs. concomitant vaccines alone. |
| End point type         | Secondary   |
| End point timeframe:   | 2 months to 13 months of age.   |

| End point values              | MenACWY3        | MenACWY4        | Routine vaccines |  |
|-------------------------------|-----------------|-----------------|------------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed   | 242             | 252             | 239              |  |
| Units: Subjects               |                 |                 |                  |  |
| number (not applicable)       |                 |                 |                  |  |
| Any AE                        | 219             | 220             | 209              |  |
| At least possibly related AEs | 24              | 32              | 10               |  |
| SAEs                          | 11              | 19              | 11               |  |

|                                       |     |     |     |  |
|---------------------------------------|-----|-----|-----|--|
| Deaths                                | 0   | 0   | 1   |  |
| Medically attended AEs                | 210 | 211 | 198 |  |
| AEs resulting in premature withdrawal | 1   | 2   | 2   |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

2 months to 13 months of age

Adverse event reporting additional description:

Solicited local and systemic and unsolicited AEs were assessed for 7 days postvaccination.

Medically attended AEs and SAEs were collected throughout the study period

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | MenACWY3 |
|-----------------------|----------|

Reporting group description:

Healthy male and female infants approximately 2 months of age received 2 infant doses at 2 and 4 months of age, with a toddler dose at 12 months of age.

|                       |          |
|-----------------------|----------|
| Reporting group title | MenACWY4 |
|-----------------------|----------|

Reporting group description:

Healthy male and female infants approximately 2 months of age received a 3-dose primary series at 2, 4 and 6 months of age and a toddler dose at 12 months of age. Approximately half of the subjects had serum collected at Month 3, and the remainder had serum collected at Month 4.

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Routine vaccines |
|-----------------------|------------------|

Reporting group description:

Healthy male and female infants approximately 2 months of age received routine vaccines including PCV-13, at 2, 4, 6 and 12 months of age.

| Serious adverse events                            | MenACWY3         | MenACWY4         | Routine vaccines |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events |                  |                  |                  |
| subjects affected / exposed                       | 11 / 242 (4.55%) | 19 / 252 (7.54%) | 11 / 239 (4.60%) |
| number of deaths (all causes)                     | 0                | 0                | 0                |
| number of deaths resulting from adverse events    | 0                | 0                | 0                |
| Injury, poisoning and procedural complications    |                  |                  |                  |
| Skull fracture                                    |                  |                  |                  |
| subjects affected / exposed                       | 1 / 242 (0.41%)  | 0 / 252 (0.00%)  | 0 / 239 (0.00%)  |
| occurrences causally related to treatment / all   | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0            | 0 / 0            |
| Congenital, familial and genetic disorders        |                  |                  |                  |
| Congenital megacolon                              |                  |                  |                  |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Krabbe's disease                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Laryngomalacia                                       |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                                    |                 |                 |                 |
| Cardio-respiratory arrest                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Nervous system disorders                             |                 |                 |                 |
| Convulsion   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 2 / 252 (0.79%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxic-ischaemic encephalopathy                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Nystagmus  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Pyrexia  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal disorders                      |                 |                 |                 |
| Anal fissure                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| Pneumomediastinum                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory acidosis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sleep apnoea syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Breath holding                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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                     |                 |                 |                 |
| Abdominal abscess                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| <b>Abscess</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| <b>Atypical pneumonia</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| <b>Bronchiolitis</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 242 (0.83%) | 2 / 252 (0.79%) | 4 / 239 (1.67%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Clostridium difficile colitis</b>            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| <b>Croup infectious</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| 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>Gastroenteritis</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastroenteritis viral</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| <b>Influenza</b>                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Otitis media acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 242 (0.41%) | 1 / 252 (0.40%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia respiratory syncytial viral           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal abscess                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 1 / 252 (0.40%) | 0 / 239 (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           |
| Respiratory syncytial virus bronchiolitis       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 242 (0.83%) | 5 / 252 (1.98%) | 2 / 239 (0.84%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Staphylococcal abscess                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Failure to thrive                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 242 (0.41%) | 0 / 252 (0.00%) | 0 / 239 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 242 (0.00%) | 0 / 252 (0.00%) | 1 / 239 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| 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>                     | MenACWY3           | MenACWY4           | Routine vaccines   |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 238 / 242 (98.35%) | 233 / 252 (92.46%) | 228 / 239 (95.40%) |
| Nervous system disorders                              |                    |                    |                    |
| Somnolence  |                    |                    |                    |
| alternative assessment type: Systematic               |                    |                    |                    |
| subjects affected / exposed                           | 162 / 242 (66.94%) | 154 / 252 (61.11%) | 158 / 239 (66.11%) |
| occurrences (all)                                     | 400                | 363                | 377                |
| General disorders and administration site conditions  |                    |                    |                    |
| Crying  |                    |                    |                    |
| subjects affected / exposed                           | 140 / 242 (57.85%) | 138 / 252 (54.76%) | 112 / 239 (46.86%) |
| occurrences (all)                                     | 227                | 259                | 220                |
| Injection site induration                             |                    |                    |                    |
| subjects affected / exposed                           | 65 / 242 (26.86%)  | 45 / 252 (17.86%)  | 79 / 239 (33.05%)  |
| occurrences (all)                                     | 93                 | 72                 | 138                |
| Injection site erythema                               |                    |                    |                    |
| alternative assessment type: Systematic               |                    |                    |                    |
| subjects affected / exposed                           | 87 / 242 (35.95%)  | 80 / 252 (31.75%)  | 89 / 239 (37.24%)  |
| occurrences (all)                                     | 139                | 164                | 160                |
| Injection site pain                                   |                    |                    |                    |
| alternative assessment type: Systematic               |                    |                    |                    |
| subjects affected / exposed                           | 137 / 242 (56.61%) | 140 / 252 (55.56%) | 138 / 239 (57.74%) |
| occurrences (all)                                     | 286                | 282                | 266                |
| Pyrexia   |                    |                    |                    |
| alternative assessment type: Systematic               |                    |                    |                    |



|   |   |   |   |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)  | 88 / 242 (36.36%)<br>138  | 88 / 252 (34.92%)<br>141  | 69 / 239 (28.87%)<br>105  |
| Ear and labyrinth disorders<br>Ear pain<br>subjects affected / exposed<br>occurrences (all)   | 13 / 242 (5.37%)<br>16  | 10 / 252 (3.97%)<br>12  | 9 / 239 (3.77%)<br>12   |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)<br><br>Teething<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 10 / 242 (4.13%)<br>11<br><br>103 / 242 (42.56%)<br>180<br><br>11 / 242 (4.55%)<br>11<br><br>15 / 242 (6.20%)<br>16<br><br>76 / 242 (31.40%)<br>127 | 21 / 252 (8.33%)<br>23<br><br>78 / 252 (30.95%)<br>143<br><br>14 / 252 (5.56%)<br>14<br><br>13 / 252 (5.16%)<br>14<br><br>68 / 252 (26.98%)<br>99 | 19 / 239 (7.95%)<br>21<br><br>80 / 239 (33.47%)<br>138<br><br>27 / 239 (11.30%)<br>30<br><br>19 / 239 (7.95%)<br>24<br><br>67 / 239 (28.03%)<br>110 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Wheezing<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 32 / 242 (13.22%)<br>33<br><br>12 / 242 (4.96%)<br>12<br><br>16 / 242 (6.61%)<br>18   | 32 / 252 (12.70%)<br>34<br><br>9 / 252 (3.57%)<br>9<br><br>18 / 252 (7.14%)<br>22   | 37 / 239 (15.48%)<br>44<br><br>16 / 239 (6.69%)<br>20<br><br>14 / 239 (5.86%)<br>18   |
| Skin and subcutaneous tissue disorders<br>Dermatitis atopic   |   |   |   |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed                | 10 / 242 (4.13%)   | 11 / 252 (4.37%)   | 14 / 239 (5.86%)   |
| occurrences (all)                          | 13                 | 12                 | 16                 |
| Eczema                                     |                    |                    |                    |
| subjects affected / exposed                | 16 / 242 (6.61%)   | 19 / 252 (7.54%)   | 20 / 239 (8.37%)   |
| occurrences (all)                          | 18                 | 19                 | 22                 |
| Dermatitis diaper                          |                    |                    |                    |
| subjects affected / exposed                | 38 / 242 (15.70%)  | 31 / 252 (12.30%)  | 22 / 239 (9.21%)   |
| occurrences (all)                          | 41                 | 38                 | 33                 |
| Rash                                       |                    |                    |                    |
| alternative assessment type:<br>Systematic |                    |                    |                    |
| subjects affected / exposed                | 29 / 242 (11.98%)  | 31 / 252 (12.30%)  | 36 / 239 (15.06%)  |
| occurrences (all)                          | 34                 | 37                 | 47                 |
| Psychiatric disorders                      |                    |                    |                    |
| Irritability                               |                    |                    |                    |
| alternative assessment type:<br>Systematic |                    |                    |                    |
| subjects affected / exposed                | 181 / 242 (74.79%) | 179 / 252 (71.03%) | 157 / 239 (65.69%) |
| occurrences (all)                          | 479                | 459                | 399                |
| Eating disorder                            |                    |                    |                    |
| alternative assessment type:<br>Systematic |                    |                    |                    |
| subjects affected / exposed                | 104 / 242 (42.98%) | 104 / 252 (41.27%) | 93 / 239 (38.91%)  |
| occurrences (all)                          | 195                | 189                | 152                |
| Infections and infestations                |                    |                    |                    |
| Conjunctivitis                             |                    |                    |                    |
| subjects affected / exposed                | 42 / 242 (17.36%)  | 25 / 252 (9.92%)   | 40 / 239 (16.74%)  |
| occurrences (all)                          | 51                 | 31                 | 44                 |
| Bronchiolitis                              |                    |                    |                    |
| subjects affected / exposed                | 34 / 242 (14.05%)  | 36 / 252 (14.29%)  | 30 / 239 (12.55%)  |
| occurrences (all)                          | 41                 | 46                 | 36                 |
| Candida nappy rash                         |                    |                    |                    |
| subjects affected / exposed                | 13 / 242 (5.37%)   | 6 / 252 (2.38%)    | 7 / 239 (2.93%)    |
| occurrences (all)                          | 14                 | 7                  | 7                  |
| Bronchitis                                 |                    |                    |                    |
| subjects affected / exposed                | 8 / 242 (3.31%)    | 19 / 252 (7.54%)   | 17 / 239 (7.11%)   |
| occurrences (all)                          | 9                  | 24                 | 18                 |
| Candidiasis                                |                    |                    |                    |

|                                   |                    |                    |                    |
|-----------------------------------|--------------------|--------------------|--------------------|
| subjects affected / exposed       | 14 / 242 (5.79%)   | 20 / 252 (7.94%)   | 21 / 239 (8.79%)   |
| occurrences (all)                 | 15                 | 23                 | 22                 |
| Croup Infectious                  |                    |                    |                    |
| subjects affected / exposed       | 13 / 242 (5.37%)   | 16 / 252 (6.35%)   | 16 / 239 (6.69%)   |
| occurrences (all)                 | 13                 | 17                 | 19                 |
| Gastroenteritis                   |                    |                    |                    |
| subjects affected / exposed       | 22 / 242 (9.09%)   | 18 / 252 (7.14%)   | 27 / 239 (11.30%)  |
| occurrences (all)                 | 26                 | 21                 | 30                 |
| Otitis media                      |                    |                    |                    |
| subjects affected / exposed       | 94 / 242 (38.84%)  | 77 / 252 (30.56%)  | 89 / 239 (37.24%)  |
| occurrences (all)                 | 193                | 153                | 183                |
| Rhinitis                          |                    |                    |                    |
| subjects affected / exposed       | 20 / 242 (8.26%)   | 17 / 252 (6.75%)   | 15 / 239 (6.28%)   |
| occurrences (all)                 | 25                 | 26                 | 20                 |
| Otitis media acute                |                    |                    |                    |
| subjects affected / exposed       | 23 / 242 (9.50%)   | 19 / 252 (7.54%)   | 16 / 239 (6.69%)   |
| occurrences (all)                 | 31                 | 24                 | 29                 |
| Sinusitis                         |                    |                    |                    |
| subjects affected / exposed       | 9 / 242 (3.72%)    | 17 / 252 (6.75%)   | 7 / 239 (2.93%)    |
| occurrences (all)                 | 10                 | 21                 | 8                  |
| Viral infection                   |                    |                    |                    |
| subjects affected / exposed       | 38 / 242 (15.70%)  | 32 / 252 (12.70%)  | 30 / 239 (12.55%)  |
| occurrences (all)                 | 42                 | 38                 | 37                 |
| Upper respiratory tract infection |                    |                    |                    |
| subjects affected / exposed       | 105 / 242 (43.39%) | 107 / 252 (42.46%) | 106 / 239 (44.35%) |
| occurrences (all)                 | 192                | 186                | 194                |
| Viral rash                        |                    |                    |                    |
| subjects affected / exposed       | 10 / 242 (4.13%)   | 10 / 252 (3.97%)   | 13 / 239 (5.44%)   |
| occurrences (all)                 | 10                 | 12                 | 14                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 05 July 2011 | A secondary objective was added to compare persistence of 2 vs 3-dose infant series at 12 months of age; 4-fold rise in hSBA added as an endpoint for evaluating immune response at 13 months of age (ie, following the toddler dose).   |
| 10 May 2012  | Added primary objective added, to demonstrate a sufficient immune response of 4 doses of MenACWY given to infants at 2, 4, 6 and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) $\geq 1:8$ , directed against N meningitidis serogroups A, C, W and Y.<br>Added description of tiered approach of assessing noninterference of PCV-13 concomitantly administered with MenACWY, using a hierarchical sequential testing procedure that groups the serotypes into 2 families. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption   | Restart date |
|--------------|--|--------------|
| 07 July 2011 | FDA/CBER imposed a formal partial clinical hold due to insufficient information to assess the risks to subjects of translucent particles detected in the prefilled syringes (PFS) used in ongoing studies. All study sites in Canada and the USA were notified via letter to immediately stop using the PFS/vial presentation, to quarantine all doses, and to immediately switch to the vial/vial vaccine presentation. | 26 July 2011 |

Notes:

### Limitations and caveats

None reported