



## Clinical trial results:

**A Phase 3, randomized, open label, controlled multi center study to evaluate the safety and immunogenicity of 4 doses of MenACWY conjugate vaccine, administered concomitantly with routine vaccines, among infants aged 2 months**

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

## Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-005061-72   |
| Trial protocol           | Outside EU/EEA   |
| Global end of trial date | 23 November 2011 |

## Results information

|                                |                                                                                                                    |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                       |
| This version publication date  | 04 June 2016                                                                                                       |
| First version publication date | 04 April 2015                                                                                                      |
| Version creation reason        | • Correction of full data set re-QC study needed because of EudraCT system glitch and updates to results required. |

## Trial information

### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | V59_33 |
|-----------------------|--------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01000311 |
| 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 Vaccine,<br>RegistryContactVaccinesUS@novartis.com |
| Scientific contact           | Posting Director, Novartis Vaccine,<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                       | 09 October 2012  |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 23 November 2011 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants in terms of the percentages of subjects with an human Serum Bacteridal Assay (hSBA)  $\geq 1:8$  at 1 month post vaccination, for each of the four meningococcal vaccine serogroups.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the latest version of the Declaration of Helsinki accepted by the local authorities, and was consistent with Good Clinical Practises (GCPs) and the applicable regulatory requirement (s) for the country in which the trial was conducted, GCPs according to International Conference on Harmonisation (ICH) guidelines, and applicable Standard Operating Procedures (SOPs).

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 19 November 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 74      |
| Country: Number of subjects enrolled | Canada: 6          |
| Country: Number of subjects enrolled | United States: 449 |
| Worldwide total number of subjects   | 529                |
| 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          | 529 |

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

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled from 42 sites in USA, 3 sites in Australia and 1 site in Canada

### Pre-assignment

Screening details:

All enrolled subjects were included in the trial

### Period 1

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

Blinding implementation details:

The trial was designed as an open-label study; both the study personnel and the subject's parent/legal guardian knew the vaccines being administered; however, randomization was done in a blinded manner. Laboratory staff were blinded to the study group allocation when processing the serologies.

### Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | MenACWY-CRM + Routine Vaccines |

Arm description:

Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

|                                        |                                                        |
|----------------------------------------|--------------------------------------------------------|
| Arm type                               | Experimental                                           |
| Investigational medicinal product name | Meningococcal Group A, C, W135 and Y conjugate vaccine |
| Investigational medicinal product code |                                                        |
| Other name                             |                                                        |
| Pharmaceutical forms                   | Powder and solution for solution for injection         |
| Routes of administration               | Intramuscular use                                      |

Dosage and administration details:

One 0.5 mL dose of MenACWY was administered by intramuscular injection in the anterolateral area of the thigh.

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

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

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

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

|                                        |                                                                  |
|----------------------------------------|------------------------------------------------------------------|
| Investigational medicinal product name | HBV vaccine                                                      |
| Investigational medicinal product code |                                                                  |
| Other name                             | Hepatitis B vaccine, Engerix-B, H-B-VAX II, RECOMBINAX, Pediarix |

|                          |                          |
|--------------------------|--------------------------|
| Pharmaceutical forms     | Suspension for injection |
| Routes of administration | Intramuscular use        |

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

|                                        |                                                |
|----------------------------------------|------------------------------------------------|
| Investigational medicinal product name | MMR                                            |
| Investigational medicinal product code |                                                |
| Other name                             | MEASLES, MUMPS, and RUBELLA VIRUS VACCINE      |
| Pharmaceutical forms                   | Powder and solution for solution for injection |
| Routes of administration               | Subcutaneous use                               |

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

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

Arm description:

Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

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

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

|                                        |                                                        |
|----------------------------------------|--------------------------------------------------------|
| Investigational medicinal product name | HBV vaccine                                            |
| Investigational medicinal product code |                                                        |
| Other name                             | Hepatitis B vaccine, Engerix-B, H-B-VAX II, RECOMBINAX |
| Pharmaceutical forms                   | Suspension for injection                               |
| Routes of administration               | Intramuscular use                                      |

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions

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

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

|                                        |                                                |
|----------------------------------------|------------------------------------------------|
| Investigational medicinal product name | MMR                                            |
| Investigational medicinal product code |                                                |
| Other name                             | MEASLES, MUMPS, and RUBELLA VIRUS VACCINE      |
| Pharmaceutical forms                   | Powder and solution for solution for injection |
| Routes of administration               | Subcutaneous use                               |

Dosage and administration details:

Routine vaccines were administered to subjects according to manufacturer instructions.

| <b>Number of subjects in period 1</b> | <b>MenACWY-CRM +<br/>Routine Vaccines</b> | <b>Routine Vaccines</b> |
|---------------------------------------|-------------------------------------------|-------------------------|
| Started                               | 258                                       | 271                     |
| Completed                             | 213                                       | 201                     |
| Not completed                         | 45                                        | 70                      |
| Consent withdrawn by subject          | 16                                        | 24                      |
| Inappropriate enrollment              | 2                                         | -                       |
| Adverse event                         | 2                                         | 5                       |
| Lost to follow-up                     | 15                                        | 24                      |
| Protocol deviation                    | 1                                         | 2                       |
| Administrative reason                 | 9                                         | 15                      |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                     |                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                               | MenACWY-CRM + Routine Vaccines |
| Reporting group description:<br>Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months. |                                |
| Reporting group title                                                                                                                                                                                                                                                                                               | Routine Vaccines               |
| Reporting group description:<br>Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.                                                                                                                                    |                                |

| Reporting group values                                | MenACWY-CRM +<br>Routine Vaccines | Routine Vaccines | Total |
|-------------------------------------------------------|-----------------------------------|------------------|-------|
| Number of subjects                                    | 258                               | 271              | 529   |
| Age categorical<br>Units: Subjects                    |                                   |                  |       |
| In utero                                              |                                   |                  | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |                                   |                  | 0     |
| Newborns (0-27 days)                                  |                                   |                  | 0     |
| Infants and toddlers (28 days-23<br>months)           |                                   |                  | 0     |
| 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                         |                                   |                  |       |
| arithmetic mean                                       | 64.7                              | 65.4             |       |
| standard deviation                                    | ± 6.5                             | ± 7.4            | -     |
| Gender categorical<br>Units: Subjects                 |                                   |                  |       |
| Female                                                | 125                               | 130              | 255   |
| Male                                                  | 133                               | 141              | 274   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                     |                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                               | MenACWY-CRM + Routine Vaccines      |
| Reporting group description:<br>Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months. |                                     |
| Reporting group title                                                                                                                                                                                                                                                                                               | Routine Vaccines                    |
| Reporting group description:<br>Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.                                                                                                                                    |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | All Enrolled Set                    |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Intention-to-treat                  |
| Subject analysis set description:<br>All subjects who have signed an informed consent, undergone screening procedures, and are randomized                                                                                                                                                                           |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Safety                              |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Safety analysis                     |
| Subject analysis set description:<br>All subjects in the exposed population who provide post-baseline safety data.                                                                                                                                                                                                  |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Exposed Set                         |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Safety analysis                     |
| Subject analysis set description:<br>All enrolled subjects who actually receive a study vaccination.                                                                                                                                                                                                                |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - Concomitant Infant   |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.                                                               |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - Pertussis Infant     |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.                                                               |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - Hepatitis B Infant   |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.                                                               |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - MenACWY Infant       |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.                                                               |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - Pneumococcal Toddler |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.                                                               |                                     |
| Subject analysis set title                                                                                                                                                                                                                                                                                          | Per Protocol - MenACWY Toddler      |
| Subject analysis set type                                                                                                                                                                                                                                                                                           | Per protocol                        |



Subject analysis set description:

All enrolled subjects who received all the relevant doses of vaccine correctly; provided evaluable serum samples at the relevant time points; had no major protocol deviation as defined prior to database lock.

**Primary: 1. Percentage of Subjects With human Serum Bactericidal Assay (hSBA) Titer  $\geq 1:8$  Against Serogroup A, C, W and Y One Month After Toddler Vaccination**

|                 |                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 1. Percentage of Subjects With human Serum Bactericidal Assay (hSBA) Titer $\geq 1:8$ Against Serogroup A, C, W and Y One Month After Toddler Vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Immunogenicity was measured as the percentage of subjects who achieved hSBA titer  $\geq 1:8$  against meningococcal serogroup A, C, W and Y, evaluated by serum bactericidal assay using human complement, at baseline and one month after toddler vaccination administered at 12 months of age. The immune response was considered sufficient if the lower limit of the two-sided 95% confidence intervals (CIs) for the percentage of subjects with hSBA titer  $\geq 1:8$ , at one month after toddler vaccination, was greater than 85% for the serogroup C, W, or Y and greater than 80% for the serogroup A.

Analysis was done on the per-protocol (PP) toddler dataset for MenACWY-CRM.

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

End point timeframe:

Baseline and one month after toddler dose (month 13).

| End point values                        | MenACWY-CRM + Routine Vaccines | Routine Vaccines |  |  |
|-----------------------------------------|--------------------------------|------------------|--|--|
| Subject group type                      | Reporting group                | Reporting group  |  |  |
| Number of subjects analysed             | 170                            | 178              |  |  |
| Units: percentage of subjects           |                                |                  |  |  |
| number (confidence interval 95%)        |                                |                  |  |  |
| Serogroup A - Baseline (N=170,178)      | 7 (4 to 12)                    | 2 (0 to 5)       |  |  |
| Serogroup A - Post-4th dose (N=168,175) | 89 (83 to 93)                  | 2 (0 to 5)       |  |  |
| Serogroup C - Baseline (N=166,174)      | 37 (30 to 45)                  | 2 (1 to 6)       |  |  |
| Serogroup C - Post-4th dose (N=156,171) | 95 (90 to 98)                  | 2 (1 to 6)       |  |  |
| Serogroup W - Baseline (N=152,164)      | 70 (62 to 77)                  | 5 (2 to 9)       |  |  |
| Serogroup W - Post-4th dose (N=153,165) | 97 (93 to 99)                  | 7 (3 to 12)      |  |  |
| Serogroup Y - Baseline (N=144,150)      | 53 (45 to 61)                  | 3 (1 to 6)       |  |  |
| Serogroup Y - Post-4th dose (N=153,159) | 96 (92 to 99)                  | 1 (0 to 4)       |  |  |

**Statistical analyses**

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

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA  $\geq 1:8$  against serogroup A at 1 month post 4th vaccination.

|                   |                                                   |
|-------------------|---------------------------------------------------|
| Comparison groups | Routine Vaccines v MenACWY-CRM + Routine Vaccines |
|-------------------|---------------------------------------------------|

|                                         |                                     |
|-----------------------------------------|-------------------------------------|
| Number of subjects included in analysis | 348                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           | non-inferiority <sup>[1]</sup>      |
| Parameter estimate                      | lower limit of the two-sided 95% CI |
| Point estimate                          | 89                                  |
| Confidence interval                     |                                     |
| level                                   | 95 %                                |
| sides                                   | 2-sided                             |
| lower limit                             | 83                                  |
| upper limit                             | 93                                  |

Notes:

[1] - Success criterion:

The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA  $\geq 1:8$ , at 1 month after the fourth dose, to be greater than 80% for serogroup A.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA  $\geq 1:8$  against serogroup C at 1 month post 4th vaccination.

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 348                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[2]</sup>                    |
| Parameter estimate                      | lower limit of the two-sided 95% CI               |
| Point estimate                          | 95                                                |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 90                                                |
| upper limit                             | 98                                                |

Notes:

[2] - Success criterion:

The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA  $\geq 1:8$ , at 1 month after the fourth dose, to be greater than 85% for serogroup C.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA  $\geq 1:8$  against serogroup W at 1 month post 4th vaccination.

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 348                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[3]</sup>                    |
| Parameter estimate                      | lower limit of the two-sided 95% CI               |
| Point estimate                          | 97                                                |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 93                                                |
| upper limit                             | 99                                                |

Notes:

[3] - Success criterion:

The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA  $\geq 1:8$ , at 1 month after the fourth dose, to be greater than 85% for serogroup W.

|                                                                                                                                                                                                                                                                 |                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                               | Statistical analysis 4                            |
| Statistical analysis description:                                                                                                                                                                                                                               |                                                   |
| The sufficiency of the immune response following 4 doses of MenACWY vaccine given at 2, 4, 6 and 12 months in healthy infants was assessed in terms of the percentages of subjects with an hSBA $\geq 1:8$ against serogroup Y at 1 month post 4th vaccination. |                                                   |
| Comparison groups                                                                                                                                                                                                                                               | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                                                                                                         | 348                                               |
| Analysis specification                                                                                                                                                                                                                                          | Pre-specified                                     |
| Analysis type                                                                                                                                                                                                                                                   | non-inferiority <sup>[4]</sup>                    |
| Parameter estimate                                                                                                                                                                                                                                              | lower limit of the two-sided 95% CI               |
| Point estimate                                                                                                                                                                                                                                                  | 96                                                |
| Confidence interval                                                                                                                                                                                                                                             |                                                   |
| level                                                                                                                                                                                                                                                           | 95 %                                              |
| sides                                                                                                                                                                                                                                                           | 2-sided                                           |
| lower limit                                                                                                                                                                                                                                                     | 92                                                |
| upper limit                                                                                                                                                                                                                                                     | 99                                                |

Notes:

[4] - Success criterion:

The lower limit of the two-sided 95% CI for the percentage of subjects with hSBA  $\geq 1:8$ , at 1 month after the fourth dose, to be greater than 85% for serogroup Y.

## Secondary: 2.hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Toddler Vaccination

|                                                                                                                                                                                                                                                                         |                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                         | 2.hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Toddler Vaccination |
| End point description:                                                                                                                                                                                                                                                  |                                                                                                         |
| Immunogenicity was measured as the hSBA GMTs directed against meningococcal serogroup A, C, W and Y, at baseline and one month after toddler vaccination administered at 12 months of age. Analysis was performed on the PP toddler dataset for MenACWY-CRM vaccination |                                                                                                         |
| End point type                                                                                                                                                                                                                                                          | Secondary                                                                                               |
| End point timeframe:                                                                                                                                                                                                                                                    |                                                                                                         |
| Baseline and one month after toddler vaccination (month 13)                                                                                                                                                                                                             |                                                                                                         |

| End point values                         | MenACWY-CRM + Routine Vaccines | Routine Vaccines    |  |  |
|------------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group     |  |  |
| Number of subjects analysed              | 168                            | 175                 |  |  |
| Units: Titers                            |                                |                     |  |  |
| geometric mean (confidence interval 95%) |                                |                     |  |  |
| Serogroup A - Baseline (N=139,145)       | 2.07 (1.98 to 2.16)            | 2.01 (1.99 to 2.03) |  |  |
| Serogroup A - Post-4th dose (N=168,175)  | 54 (44 to 67)                  | 1.87 (1.55 to 2.27) |  |  |
| Serogroup C - Baseline (N=126,136)       | 2.49 (2.2 to 2.83)             | 2.44 (2.2 to 2.7)   |  |  |

|                                         |                     |                     |  |  |
|-----------------------------------------|---------------------|---------------------|--|--|
| Serogroup C - Post-4th dose (N=156,171) | 135 (107 to 171)    | 1.94 (1.56 to 2.4)  |  |  |
| Serogroup W - Baseline (N=113,126)      | 2.99 (2.49 to 3.6)  | 2.97 (2.52 to 3.51) |  |  |
| Serogroup W - Post-4th dose (N=153,165) | 215 (167 to 277)    | 2.15 (1.77 to 2.6)  |  |  |
| Serogroup Y - Baseline (N=108,113)      | 2.43 (2.19 to 2.71) | 2.32 (2.13 to 2.52) |  |  |
| Serogroup Y - Post-4th dose (N=153,159) | 185 (148 to 233)    | 1.89 (1.56 to 2.29) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 3. Percentage of Subjects With hSBA Titers $\geq 1:8$ and Four-Fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

|                 |                                                                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 3. Percentage of Subjects With hSBA Titers $\geq 1:8$ and Four-Fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Immunogenicity was measured as the percentage of subjects with hSBA titers  $\geq 1:8$  against meningococcal serogroup A, C, W and Y, at baseline and one month after three infant doses of vaccines administered at 2, 4 and 6 months of age.

Percentage of subjects who achieved at least four-fold rise in hSBA titers against serogroup A, C, W and Y was measured one month after three doses of infant series vaccination.

Analysis was performed on the PP dataset of MenACWY-CRM infant vaccination series.

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

End point timeframe:

Baseline and one month after three doses of infant vaccination

| End point values                                        | MenACWY-CRM + Routine Vaccines | Routine Vaccines |  |  |
|---------------------------------------------------------|--------------------------------|------------------|--|--|
| Subject group type                                      | Reporting group                | Reporting group  |  |  |
| Number of subjects analysed                             | 202                            | 208              |  |  |
| Units: Percentage of subjects                           |                                |                  |  |  |
| number (confidence interval 95%)                        |                                |                  |  |  |
| Serogroup A - hSBA $\geq 1:8$ -Baseline (N=170,178)     | 2 (0 to 5)                     | 1 (0.014 to 3)   |  |  |
| Serogroup A - hSBA $\geq 1:8$ -Post-3rd dose(N=202,208) | 76 (69 to 81)                  | 1 (0 to 4)       |  |  |
| Serogroup C - hSBA $\geq 1:8$ - Baseline(N=166,174)     | 7 (3 to 12)                    | 7 (4 to 12)      |  |  |
| Serogroup C - hSBA $\geq 1:8$ -Post-3rd dose(N=199,206) | 94 (90 to 97)                  | 1 (0 to 4)       |  |  |
| Serogroup W - hSBA $\geq 1:8$ - Baseline(N=152,164)     | 13 (8 to 20)                   | 15 (10 to 21)    |  |  |
| Serogroup W - hSBA $\geq 1:8$ -Post-3rd dose(N=194,202) | 98 (95 to 99)                  | 3 (1 to 7)       |  |  |
| Serogroup Y - hSBA $\geq 1:8$ - Baseline(N=144,150)     | 8 (4 to 13)                    | 4 (1 to 9)       |  |  |

|                                                         |               |            |  |  |
|---------------------------------------------------------|---------------|------------|--|--|
| Serogroup Y - hSBA $\geq 1:8$ -Post-3rd dose(N=188,196) | 94 (89 to 97) | 3 (1 to 6) |  |  |
| Serogroup A - 4-fold rise-Post-3rd dose(N=170,177)      | 78 (71 to 84) | 2 (0 to 5) |  |  |
| Serogroup C - 4-fold rise-Post-3rd dose(N=164,171)      | 94 (89 to 97) | 1 (0 to 4) |  |  |
| Serogroup W - 4-fold rise-Post-3rd dose(N=147,158)      | 93 (87 to 96) | 2 (0 to 5) |  |  |
| Serogroup Y -4-fold rise-Post-3rd dose(N=135,142)       | 93 (87 to 96) | 2 (0 to 6) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 4. hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | 4. hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y One Month After Three Doses Infant Series Vaccination |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

End point description:

Immunogenicity was measured as the hSBA GMTs directed against meningococcal serogroups A, C, W and Y before (baseline) and one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age.

Analysis was performed on the PP dataset of MenACWY-CRM infant vaccination series.

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

End point timeframe:

Baseline and one month after three doses of infant series vaccination

| End point values                         | MenACWY-CRM + Routine Vaccines | Routine Vaccines    |  |  |
|------------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group     |  |  |
| Number of subjects analysed              | 202                            | 209                 |  |  |
| Units: Titers                            |                                |                     |  |  |
| geometric mean (confidence interval 95%) |                                |                     |  |  |
| Serogroup A - Baseline (N=170,178)       | 2.09 (2 to 2.18)               | 2.05 (1.98 to 2.12) |  |  |
| Serogroup A - Post-3rd dose (N=202,208)  | 21 (17 to 26)                  | 2.08 (1.99 to 2.17) |  |  |
| Serogroup C - Baseline (N=166,174)       | 2.49 (2.25 to 2.76)            | 2.39 (2.18 to 2.61) |  |  |
| Serogroup C - Post-3rd dose (N=199,206)  | 74 (62 to 87)                  | 1.94 (1.64 to 2.3)  |  |  |
| Serogroup W - Baseline (N=152,164)       | 2.94 (2.52 to 3.43)            | 2.98 (2.58 to 3.45) |  |  |
| Serogroup W - Post-3rd dose (N=194,202)  | 79 (67 to 92)                  | 1.94 (1.68 to 2.24) |  |  |
| Serogroup Y - Baseline (N=144,150)       | 2.52 (2.28 to 2.77)            | 2.26 (2.12 to 2.41) |  |  |
| Serogroup Y - Post-3rd dose (N=188,196)  | 51 (43 to 61)                  | 2.13 (2.02 to 2.25) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: 5. Percentage of Subjects With Immune Response to Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

|                 |                                                                                                                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 5. Percentage of Subjects With Immune Response to Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

The percentages of subjects with pre-specified cut-off limit of  $\geq 0.1$  IU/mL (Diphtheria and Tetanus);  $\geq 0.15$   $\mu$ g/mL (Hib);  $\geq 0.35$   $\mu$ g/mL (Pneumococcal antigens, PnC); and  $\geq 10$  mIU/mL (Hepatitis B) was evaluated using enzyme-linked immunosorbent assay (ELISA) at one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age.

The percentage of subjects with immune response against pertussis antigens (PT, FHA, Pertactin, FIM) (initially seronegative infants,  $\geq 4$  times the lower limit of quantification (LLQ); initially seropositive infants, at least 4 times prevaccination concentration) was measured by ELISA and percentage of subjects with titer  $\geq 1:8$  (Polio types 1,2,3) by neutralization test (NT) one month after three doses of infant series vaccination administered at 2, 4 and 6 months of age. Analysis was performed on the PP concomitant infant population.

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

#### End point timeframe:

One month after three doses of infant series vaccination

| End point values                             | MenACWY-CRM + Routine Vaccines | Routine Vaccines |  |  |
|----------------------------------------------|--------------------------------|------------------|--|--|
| Subject group type                           | Reporting group                | Reporting group  |  |  |
| Number of subjects analysed                  | 207                            | 218              |  |  |
| Units: Percentage of subjects                |                                |                  |  |  |
| number (confidence interval 95%)             |                                |                  |  |  |
| Diphtheria ( $\geq 0.1$ IU/mL)               | 99 (96 to 100)                 | 99 (96 to 100)   |  |  |
| Tetanus ( $\geq 0.1$ IU/mL)                  | 97 (94 to 99)                  | 97 (93 to 99)    |  |  |
| PT (N=185,191)                               | 77 (71 to 83)                  | 81 (75 to 86)    |  |  |
| FHA (N=185,191)                              | 70 (63 to 76)                  | 65 (58 to 72)    |  |  |
| Pertactin (N=185,191)                        | 73 (66 to 79)                  | 73 (66 to 79)    |  |  |
| FIM (N=185,191)                              | 74 (67 to 80)                  | 76 (69 to 82)    |  |  |
| Polio Type 1 - $\geq 1:8$ (N=115,113)        | 99 (95 to 100)                 | 98 (94 to 100)   |  |  |
| Polio Type 2 - $\geq 1:8$ (N=185,179)        | 100 (98 to 100)                | 99 (97 to 100)   |  |  |
| Polio Type 3 - $\geq 1:8$ (N=164,162)        | 99 (97 to 100)                 | 100 (98 to 100)  |  |  |
| Hepatitis B - $\geq 10$ mIU/mL (N=138,148)   | 96 (92 to 99)                  | 97 (92 to 99)    |  |  |
| PRP-Hib - $\geq 0.15$ $\mu$ g/mL (N=187,194) | 95 (90 to 97)                  | 89 (84 to 93)    |  |  |

|                                                    |                 |                |  |  |
|----------------------------------------------------|-----------------|----------------|--|--|
| PnC 4 - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178)   | 99 (96 to 100)  | 98 (94 to 99)  |  |  |
| PnC 6B - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178)  | 86 (80 to 91)   | 90 (84 to 94)  |  |  |
| PnC 9V - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178)  | 91 (86 to 95)   | 94 (90 to 97)  |  |  |
| PnC 14 - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178)  | 99 (96 to 100)  | 99 (96 to 100) |  |  |
| PnC 18C - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178) | 95 (90 to 97)   | 97 (94 to 99)  |  |  |
| PnC 19F - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178) | 100 (98 to 100) | 97 (93 to 99)  |  |  |
| PnC 23F - $\geq 0.35$ $\mu\text{g/mL}$ (N=183,178) | 89 (83 to 93)   | 94 (89 to 97)  |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                            | statistical analysis 1                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                     |                                                   |
| To demonstrate the non-inferiority of immune response to diphtheria toxin, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                     | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                               | 425                                               |
| Analysis specification                                                                                                                                                | Pre-specified                                     |
| Analysis type                                                                                                                                                         | non-inferiority <sup>[5]</sup>                    |
| Method                                                                                                                                                                | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                    | vaccine group difference                          |
| Point estimate                                                                                                                                                        | 0                                                 |
| Confidence interval                                                                                                                                                   |                                                   |
| level                                                                                                                                                                 | 95 %                                              |
| sides                                                                                                                                                                 | 2-sided                                           |
| lower limit                                                                                                                                                           | -2.9                                              |
| upper limit                                                                                                                                                           | 2.6                                               |

Notes:

[5] - Success criterion:

The immune response to diphtheria toxin, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                         | Statistical analysis 2                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                  |                                                   |
| To demonstrate the non-inferiority of immune response to tetanus toxin, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                  | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                            | 425                                               |
| Analysis specification                                                                                                                                             | Pre-specified                                     |
| Analysis type                                                                                                                                                      | non-inferiority <sup>[6]</sup>                    |
| Method                                                                                                                                                             | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                 | vaccine group difference                          |
| Point estimate                                                                                                                                                     | 0                                                 |
| Confidence interval                                                                                                                                                |                                                   |
| level                                                                                                                                                              | 95 %                                              |
| sides                                                                                                                                                              | 2-sided                                           |
| lower limit                                                                                                                                                        | -3.3                                              |
| upper limit                                                                                                                                                        | 3.9                                               |

Notes:

[6] - Success criterion:

The immune response to tetanus toxin, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                                | Statistical analysis 3                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                         |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis toxin (PT), when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                         | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                   | 425                                               |
| Analysis specification                                                                                                                                                    | Pre-specified                                     |
| Analysis type                                                                                                                                                             | non-inferiority <sup>[7]</sup>                    |
| Method                                                                                                                                                                    | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                        | vaccine group difference                          |
| Point estimate                                                                                                                                                            | -4                                                |
| Confidence interval                                                                                                                                                       |                                                   |
| level                                                                                                                                                                     | 95 %                                              |
| sides                                                                                                                                                                     | 2-sided                                           |
| lower limit                                                                                                                                                               | -12.1                                             |
| upper limit                                                                                                                                                               | 4.3                                               |

Notes:

[7] - Success criterion:

The immune response to pertussis toxin (PT), when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                                 | Statistical analysis 4                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                          |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis FHA antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                          | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                    | 425                                               |
| Analysis specification                                                                                                                                                     | Pre-specified                                     |
| Analysis type                                                                                                                                                              | non-inferiority <sup>[8]</sup>                    |
| Method                                                                                                                                                                     | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                         | vaccine group difference                          |
| Point estimate                                                                                                                                                             | 4                                                 |
| Confidence interval                                                                                                                                                        |                                                   |
| level                                                                                                                                                                      | 95 %                                              |
| sides                                                                                                                                                                      | 2-sided                                           |
| lower limit                                                                                                                                                                | -5.1                                              |
| upper limit                                                                                                                                                                | 13.6                                              |

Notes:

[8] - Success criterion:

The immune response to pertussis FHA antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                                       | Statistical analysis 5 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis description:                                                                                                                                                |                        |
| To demonstrate the non-inferiority of immune response to pertussis pertactin antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                        |



|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[9]</sup>                    |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | 0                                                 |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | -8.8                                              |
| upper limit                             | 9.1                                               |

Notes:

[9] - Success criterion:

The immune response to pertussis pertactin antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                                                                                                                                                            |                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                          | Statistical analysis 6                            |
| Statistical analysis description:                                                                                                                                          |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis FIM antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                          | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                    | 425                                               |
| Analysis specification                                                                                                                                                     | Pre-specified                                     |
| Analysis type                                                                                                                                                              | non-inferiority <sup>[10]</sup>                   |
| Method                                                                                                                                                                     | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                         | vaccine group difference                          |
| Point estimate                                                                                                                                                             | -2                                                |
| Confidence interval                                                                                                                                                        |                                                   |
| level                                                                                                                                                                      | 95 %                                              |
| sides                                                                                                                                                                      | 2-sided                                           |
| lower limit                                                                                                                                                                | -10.6                                             |
| upper limit                                                                                                                                                                | 6.8                                               |

Notes:

[10] - Success criterion:

The immune response to pertussis FIM antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                                                                                                                                                                        |                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                      | Statistical analysis 7                            |
| Statistical analysis description:                                                                                                                                                      |                                                   |
| To demonstrate the non-inferiority of immune response to hepatitis B antigen, when hepatitis B vaccine is given with MenACWY-CRM compared with when hepatitis B vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                                      | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                                | 425                                               |
| Analysis specification                                                                                                                                                                 | Pre-specified                                     |
| Analysis type                                                                                                                                                                          | non-inferiority <sup>[11]</sup>                   |
| Method                                                                                                                                                                                 | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                                     | vaccine group difference                          |
| Point estimate                                                                                                                                                                         | 0                                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -5.2    |
| upper limit         | 4.5     |

Notes:

[11] - Success criterion:

The immune response to hepatitis B antigen, when hepatitis B vaccine is given concomitantly with MenACWY-CRM, was considered non-inferior to that of hepatitis B vaccine given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 8 |
|-----------------------------------|------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to Hib antigen, when Hib vaccine is given with MenACWY-CRM compared with when Hib vaccine is given alone.

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[12]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | 5                                                 |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 0                                                 |
| upper limit                             | 11.2                                              |

Notes:

[12] - Success criterion:

The immune response to Hib vaccine, when given concomitantly with MenACWY-CRM, was considered non-inferior to that of Hib vaccine given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 9 |
|-----------------------------------|------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to polio antigen (Type 1), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[13]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | 1                                                 |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | -3.1                                              |
| upper limit                             | 5.4                                               |

Notes:

[13] - Success criterion:

The immune response to polio antigen (Type 1), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the

difference in the percentage of subjects with antibody response was greater than or equal to -5%.

| Statistical analysis title                                                                                                                                         | Statistical analysis 10                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                  |                                                   |
| To demonstrate the non-inferiority of immune response to polio antigen (Type 2), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone |                                                   |
| Comparison groups                                                                                                                                                  | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                            | 425                                               |
| Analysis specification                                                                                                                                             | Pre-specified                                     |
| Analysis type                                                                                                                                                      | non-inferiority <sup>[14]</sup>                   |
| Method                                                                                                                                                             | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                 | vaccine group difference                          |
| Point estimate                                                                                                                                                     | 1                                                 |
| Confidence interval                                                                                                                                                |                                                   |
| level                                                                                                                                                              | 95 %                                              |
| sides                                                                                                                                                              | 2-sided                                           |
| lower limit                                                                                                                                                        | -1.4                                              |
| upper limit                                                                                                                                                        | 3                                                 |

Notes:

[14] - Success criterion:

The immune response to polio antigen (Type 2), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -5%.

| Statistical analysis title                                                                                                                                         | Statistical analysis 11                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                  |                                                   |
| To demonstrate the non-inferiority of immune response to polio antigen (Type 3), when IPV routine is given with MenACWY-CRM, compared with when IPV is given alone |                                                   |
| Comparison groups                                                                                                                                                  | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                            | 425                                               |
| Analysis specification                                                                                                                                             | Pre-specified                                     |
| Analysis type                                                                                                                                                      | non-inferiority <sup>[15]</sup>                   |
| Method                                                                                                                                                             | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                 | vaccine group difference                          |
| Point estimate                                                                                                                                                     | -1                                                |
| Confidence interval                                                                                                                                                |                                                   |
| level                                                                                                                                                              | 95 %                                              |
| sides                                                                                                                                                              | 2-sided                                           |
| lower limit                                                                                                                                                        | -3.3                                              |
| upper limit                                                                                                                                                        | 1.7                                               |

Notes:

[15] - Success criterion:

The immune response to polio antigen (Type 3), when IPV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of IPV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -5%.

| Statistical analysis title                                                                                                                                     | Statistical analysis 12                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                              |                                                   |
| To demonstrate the non-inferiority of immune response to pneumococcal PnC 4 antigen, when PCV is given with MenACWY-CRM, compared with when PCV is given alone |                                                   |
| Comparison groups                                                                                                                                              | MenACWY-CRM + Routine Vaccines v Routine Vaccines |

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Number of subjects included in analysis | 425                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[16]</sup> |
| Method                                  | Miettinen and Nurminen          |
| Parameter estimate                      | vaccine group difference        |
| Point estimate                          | 1                               |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -1.9                            |
| upper limit                             | 4.6                             |

Notes:

[16] - Success criterion:

The immune response to pneumococcal PnC 4 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 13 |
|-----------------------------------|-------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 6B antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[17]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | -4                                                |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | -10.3                                             |
| upper limit                             | 3.2                                               |

Notes:

[17] - Success criterion:

The immune response to pneumococcal PnC 6B antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 14 |
|-----------------------------------|-------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 9V antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[18]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | -3                                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -8.7    |
| upper limit         | 2.3     |

Notes:

[18] - Success criterion:

The immune response to pneumococcal PnC 9V antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 15 |
|-----------------------------------|-------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 14 antigen, when Pneumococcal Veccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[19]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | 0                                                 |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | -2.8                                              |
| upper limit                             | 3                                                 |

Notes:

[19] - Success criterion:

The immune response to pneumococcal PnC 14 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 16 |
|-----------------------------------|-------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of immune response to pneumococcal PnC 18C antigen, when Pneumococcal Vaccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 425                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[20]</sup>                   |
| Method                                  | Miettinen and Nurminen                            |
| Parameter estimate                      | vaccine group difference                          |
| Point estimate                          | -3                                                |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | -7.3                                              |
| upper limit                             | 1.6                                               |

Notes:

[20] - Success criterion:

The immune response to pneumococcal PnC 18C antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                                              | Statistical analysis 17                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                                       |                                                   |
| To demonstrate the non-inferiority of immune response to pneumococcal PnC 19F antigen, when Pneumococcal Vaccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone |                                                   |
| Comparison groups                                                                                                                                                                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                                 | 425                                               |
| Analysis specification                                                                                                                                                                  | Pre-specified                                     |
| Analysis type                                                                                                                                                                           | non-inferiority <sup>[21]</sup>                   |
| Method                                                                                                                                                                                  | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                                      | vaccine group difference                          |
| Point estimate                                                                                                                                                                          | 3                                                 |
| Confidence interval                                                                                                                                                                     |                                                   |
| level                                                                                                                                                                                   | 95 %                                              |
| sides                                                                                                                                                                                   | 2-sided                                           |
| lower limit                                                                                                                                                                             | 1.3                                               |
| upper limit                                                                                                                                                                             | 7.1                                               |

Notes:

[21] - Success criterion:

The immune response to pneumococcal PnC 19F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

| Statistical analysis title                                                                                                                                                              | Statistical analysis 18                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                                       |                                                   |
| To demonstrate the non-inferiority of immune response to pneumococcal PnC 23F antigen, when Pneumococcal Vaccine (PCV) is given with MenACWY-CRM, compared with when PCV is given alone |                                                   |
| Comparison groups                                                                                                                                                                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                                 | 425                                               |
| Analysis specification                                                                                                                                                                  | Pre-specified                                     |
| Analysis type                                                                                                                                                                           | non-inferiority <sup>[22]</sup>                   |
| Method                                                                                                                                                                                  | Miettinen and Nurminen                            |
| Parameter estimate                                                                                                                                                                      | vaccine group difference                          |
| Point estimate                                                                                                                                                                          | -5                                                |
| Confidence interval                                                                                                                                                                     |                                                   |
| level                                                                                                                                                                                   | 95 %                                              |
| sides                                                                                                                                                                                   | 2-sided                                           |
| lower limit                                                                                                                                                                             | -11.4                                             |
| upper limit                                                                                                                                                                             | 0.5                                               |

Notes:

[22] - Success criterion:

The immune response to pneumococcal PnC 23F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the difference in the percentage of subjects with antibody response was greater than or equal to -10%.

## Secondary: 6. Geometric Mean Concentrations (GMCs) of Antibodies Against Routine

# Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 6. Geometric Mean Concentrations (GMCs) of Antibodies Against Routine Concomitant Vaccinations One Month After Infant Series, When Routine Vaccines Are Administered With MenACWY-CRM Compared With When Routine Vaccines Are Given Alone |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                           |
| The immune response was measured as the GMCs of antibodies directed against diphtheria, tetanus, pertussis (PT, FHA, Pertactin, FIM), hepatitis B, Hib, polio (type 1, 2 and 3) and pneumococcal (PnC 4, 6B, 9V, 14, 18C, 19F and 23F) antigens when routine vaccines are administered concomitantly with MenACWY-CRM compared with when routine vaccines are given alone, one month after three doses of infant series vaccination at 2, 4 and 6 months of age.<br>Analysis was performed on the PP concomitant infants population. |                                                                                                                                                                                                                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                                                                                                                                                                                                                                 |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                           |
| One month after three doses of infant series vaccination                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                           |

| End point values                         | MenACWY-CRM + Routine Vaccines | Routine Vaccines    |  |  |
|------------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group     |  |  |
| Number of subjects analysed              | 207                            | 218                 |  |  |
| Units: µg/mL                             |                                |                     |  |  |
| geometric mean (confidence interval 95%) |                                |                     |  |  |
| Diphtheria                               | 0.7 (0.63 to 0.78)             | 0.85 (0.76 to 0.94) |  |  |
| Tetanus                                  | 0.8 (0.7 to 0.91)              | 0.67 (0.59 to 0.76) |  |  |
| PT (N=185,191)                           | 25 (21 to 30)                  | 24 (21 to 29)       |  |  |
| FHA (N=185,191)                          | 48 (43 to 54)                  | 47 (42 to 52)       |  |  |
| Pertactin (N=185,191)                    | 56 (47 to 65)                  | 54 (46 to 62)       |  |  |
| FIM (N=185,191)                          | 133 (113 to 157)               | 122 (105 to 143)    |  |  |
| Polio Type 1 (N=115,113)                 | 149 (115 to 194)               | 117 (89 to 152)     |  |  |
| Polio Type 2 (N=185,179)                 | 210 (178 to 246)               | 185 (156 to 218)    |  |  |
| Polio Type 3 (N=164,162)                 | 457 (367 to 569)               | 402 (321 to 504)    |  |  |
| Hepatitis B (N=138,148)                  | 394 (284 to 546)               | 402 (289 to 558)    |  |  |
| Hib (N=187,194)                          | 3.75 (2.92 to 4.82)            | 2.76 (2.16 to 3.53) |  |  |
| PnC 4 (N=183,178)                        | 1.3 (1.16 to 1.46)             | 1.45 (1.29 to 1.63) |  |  |
| PnC 6B (N=183,178)                       | 1.42 (1.17 to 1.72)            | 1.79 (1.47 to 2.18) |  |  |
| PnC 9V (N=183,178)                       | 0.95 (0.84 to 1.08)            | 1.2 (1.05 to 1.36)  |  |  |
| PnC 14 (N=183,178)                       | 6.31 (5.45 to 7.31)            | 6.61 (5.69 to 7.68) |  |  |
| PnC 18C (N=183,178)                      | 1.36 (1.2 to 1.55)             | 1.42 (1.24 to 1.62) |  |  |

|                     |                     |                     |  |  |
|---------------------|---------------------|---------------------|--|--|
| PnC 19F (N=183,178) | 1.84 (1.63 to 2.08) | 2.04 (1.8 to 2.32)  |  |  |
| PnC 23F (N=183,178) | 1.15 (0.99 to 1.35) | 1.33 (1.13 to 1.56) |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                | Statistical analysis 1                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                         |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis toxin (PT), when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                         | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                   | 425                                               |
| Analysis specification                                                                                                                                                    | Pre-specified                                     |
| Analysis type                                                                                                                                                             | non-inferiority <sup>[23]</sup>                   |
| Method                                                                                                                                                                    | ANOVA                                             |
| Parameter estimate                                                                                                                                                        | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                            | 1.02                                              |
| Confidence interval                                                                                                                                                       |                                                   |
| level                                                                                                                                                                     | 95 %                                              |
| sides                                                                                                                                                                     | 2-sided                                           |
| lower limit                                                                                                                                                               | 0.81                                              |
| upper limit                                                                                                                                                               | 1.28                                              |

Notes:

[23] - Success criterion:

The immune response measured as GMC of antibodies to pertussis toxin (PT), when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67

| Statistical analysis title                                                                                                                                                 | Statistical analysis 2                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                                          |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis FHA antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                          | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                    | 425                                               |
| Analysis specification                                                                                                                                                     | Pre-specified                                     |
| Analysis type                                                                                                                                                              | non-inferiority <sup>[24]</sup>                   |
| Method                                                                                                                                                                     | ANOVA                                             |
| Parameter estimate                                                                                                                                                         | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                             | 1.04                                              |
| Confidence interval                                                                                                                                                        |                                                   |
| level                                                                                                                                                                      | 95 %                                              |
| sides                                                                                                                                                                      | 2-sided                                           |
| lower limit                                                                                                                                                                | 0.9                                               |
| upper limit                                                                                                                                                                | 1.19                                              |

Notes:

[24] - Success criterion:

The immune response measured as GMC of antibodies to pertussis FHA antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.



|                                                                                                                                                                                  |                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                | Statistical analysis 3                            |
| Statistical analysis description:                                                                                                                                                |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis pertactin antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                                | Routine Vaccines v MenACWY-CRM + Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                          | 425                                               |
| Analysis specification                                                                                                                                                           | Pre-specified                                     |
| Analysis type                                                                                                                                                                    | non-inferiority <sup>[25]</sup>                   |
| Method                                                                                                                                                                           | ANOVA                                             |
| Parameter estimate                                                                                                                                                               | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                                   | 1.04                                              |
| Confidence interval                                                                                                                                                              |                                                   |
| level                                                                                                                                                                            | 95 %                                              |
| sides                                                                                                                                                                            | 2-sided                                           |
| lower limit                                                                                                                                                                      | 0.84                                              |
| upper limit                                                                                                                                                                      | 1.28                                              |

Notes:

[25] - Success criterion:

The immune response measured as GMC of antibodies to pertussis pertactin antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.

|                                                                                                                                                                            |                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                          | Statistical analysis 4                            |
| Statistical analysis description:                                                                                                                                          |                                                   |
| To demonstrate the non-inferiority of immune response to pertussis FIM antigen, when DTaP vaccine is given with MenACWY-CRM compared with when DTaP vaccine is given alone |                                                   |
| Comparison groups                                                                                                                                                          | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                                    | 425                                               |
| Analysis specification                                                                                                                                                     | Pre-specified                                     |
| Analysis type                                                                                                                                                              | non-inferiority <sup>[26]</sup>                   |
| Method                                                                                                                                                                     | ANOVA                                             |
| Parameter estimate                                                                                                                                                         | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                             | 1.09                                              |
| Confidence interval                                                                                                                                                        |                                                   |
| level                                                                                                                                                                      | 95 %                                              |
| sides                                                                                                                                                                      | 2-sided                                           |
| lower limit                                                                                                                                                                | 0.88                                              |
| upper limit                                                                                                                                                                | 1.35                                              |

Notes:

[26] - Success criterion:

The immune response measured as GMC of antibodies to pertussis FIM antigen, when DTaP is given concomitantly with MenACWY-CRM, was considered non-inferior to that of DTaP given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Routine Vaccines group divided by GMC of Routine Vaccines group) was greater than 0.67.

## Secondary: 7. GMCs of Antibodies Against Pneumococcal Antigens One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone

|                 |                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------|
| End point title | 7. GMCs of Antibodies Against Pneumococcal Antigens One Month After Toddler Vaccination With PCV Administered With |
|-----------------|--------------------------------------------------------------------------------------------------------------------|

## End point description:

Immunogenicity was measured as the GMCs of anti-pneumococcal antibodies against pneumococcal antigens PnC 4, 6B, 9V, 14, 18C, 19F and 23F, one month after toddler dose of PCV at 12 months of age administered concomitantly with MenACWY-CRM compared with PCV given alone. Analysis was performed on the PP pneumococcal toddler population.

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

## End point timeframe:

One month after PCV toddler vaccination

| End point values                         | MenACWY-CRM + Routine Vaccines | Routine Vaccines    |  |  |
|------------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type                       | Reporting group                | Reporting group     |  |  |
| Number of subjects analysed              | 161                            | 170                 |  |  |
| Units: µg/mL                             |                                |                     |  |  |
| geometric mean (confidence interval 95%) |                                |                     |  |  |
| PnC 4                                    | 1.57 (1.35 to 1.82)            | 1.6 (1.39 to 1.85)  |  |  |
| PnC 6B                                   | 5.92 (5.05 to 6.95)            | 7.8 (6.69 to 9.09)  |  |  |
| PnC 9V                                   | 1.67 (1.44 to 1.93)            | 1.91 (1.66 to 2.19) |  |  |
| PnC 14                                   | 7.9 (6.73 to 9.28)             | 7.61 (6.52 to 8.88) |  |  |
| PnC 18C                                  | 1.79 (1.55 to 2.08)            | 1.8 (1.57 to 2.08)  |  |  |
| PnC 19F                                  | 5.03 (4.36 to 5.82)            | 5.68 (4.95 to 6.53) |  |  |
| PnC 23F                                  | 3.3 (2.8 to 3.89)              | 3.91 (3.34 to 4.57) |  |  |

## Statistical analyses

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

## Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 4 antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | Routine Vaccines v MenACWY-CRM + Routine Vaccines |
| Number of subjects included in analysis | 331                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[27]</sup>                   |
| Method                                  | ANOVA                                             |
| Parameter estimate                      | vaccine group ratio of GMCs                       |
| Point estimate                          | 0.98                                              |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 0.8                                               |
| upper limit                             | 1.19                                              |

Notes:

[27] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 4 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

| Statistical analysis title                                                                                                                                      | Statistical analysis 2                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                               |                                                   |
| To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 6B antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone |                                                   |
| Comparison groups                                                                                                                                               | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                         | 331                                               |
| Analysis specification                                                                                                                                          | Pre-specified                                     |
| Analysis type                                                                                                                                                   | non-inferiority <sup>[28]</sup>                   |
| Method                                                                                                                                                          | ANOVA                                             |
| Parameter estimate                                                                                                                                              | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                  | 0.76                                              |
| Confidence interval                                                                                                                                             |                                                   |
| level                                                                                                                                                           | 95 %                                              |
| sides                                                                                                                                                           | 2-sided                                           |
| lower limit                                                                                                                                                     | 0.62                                              |
| upper limit                                                                                                                                                     | 0.93                                              |

Notes:

[28] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 6B antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50

| Statistical analysis title                                                                                                                                      | Statistical analysis 3                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| Statistical analysis description:                                                                                                                               |                                                   |
| To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 9V antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone |                                                   |
| Comparison groups                                                                                                                                               | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis                                                                                                                         | 331                                               |
| Analysis specification                                                                                                                                          | Pre-specified                                     |
| Analysis type                                                                                                                                                   | non-inferiority <sup>[29]</sup>                   |
| Method                                                                                                                                                          | ANOVA                                             |
| Parameter estimate                                                                                                                                              | vaccine group ratio of GMCs                       |
| Point estimate                                                                                                                                                  | 0.87                                              |
| Confidence interval                                                                                                                                             |                                                   |
| level                                                                                                                                                           | 95 %                                              |
| sides                                                                                                                                                           | 2-sided                                           |
| lower limit                                                                                                                                                     | 0.72                                              |
| upper limit                                                                                                                                                     | 1.06                                              |

Notes:

[29] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 9V antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

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

---

**Statistical analysis description:**

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 14 antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 331                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[30]</sup>                   |
| Method                                  | ANOVA                                             |
| Parameter estimate                      | vaccine group ratio of GMCs                       |
| Point estimate                          | 1.04                                              |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 0.84                                              |
| upper limit                             | 1.28                                              |

**Notes:**

[30] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 14 antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

---

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 5 |
|-----------------------------------|------------------------|

**Statistical analysis description:**

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 18C antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone.

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 331                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[31]</sup>                   |
| Method                                  | ANOVA                                             |
| Parameter estimate                      | vaccine group ratio of GMCs                       |
| Point estimate                          | 0.99                                              |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 0.82                                              |
| upper limit                             | 1.2                                               |

**Notes:**

[31] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 18C antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

---

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 6 |
|-----------------------------------|------------------------|

**Statistical analysis description:**

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 19F antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

|                   |                                                   |
|-------------------|---------------------------------------------------|
| Comparison groups | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
|-------------------|---------------------------------------------------|

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Number of subjects included in analysis | 331                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | non-inferiority <sup>[32]</sup> |
| Method                                  | ANOVA                           |
| Parameter estimate                      | vaccine group ratio of GMCs     |
| Point estimate                          | 0.89                            |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | 0.73                            |
| upper limit                             | 1.07                            |

Notes:

[32] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 19F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical analysis 7 |
|-----------------------------------|------------------------|

Statistical analysis description:

To demonstrate the non-inferiority of GMC of antibodies to pneumococcal PnC 23F antigen when PCV is given with MenACWY-CRM compared with when PCV is given alone

|                                         |                                                   |
|-----------------------------------------|---------------------------------------------------|
| Comparison groups                       | MenACWY-CRM + Routine Vaccines v Routine Vaccines |
| Number of subjects included in analysis | 331                                               |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | non-inferiority <sup>[33]</sup>                   |
| Method                                  | ANOVA                                             |
| Parameter estimate                      | vaccine group ratio of GMCs                       |
| Point estimate                          | 0.84                                              |
| Confidence interval                     |                                                   |
| level                                   | 95 %                                              |
| sides                                   | 2-sided                                           |
| lower limit                             | 0.68                                              |
| upper limit                             | 1.04                                              |

Notes:

[33] - Success criterion:

The immune response as GMC of antibodies to pneumococcal PnC 23F antigen, when PCV is given concomitantly with MenACWY-CRM, was considered non-inferior to that of PCV given alone, if the lower limit of the two-sided 95% CI for the ratio of GMCs (GMC of MenACWY-CRM + Prevnar group divided by GMC of Prevnar group) was greater than 0.50.

## **Secondary: 8. Percentage of Subjects With Anti-pneumococcal Antigen Antibodies $\geq 0.35$ $\mu\text{g/mL}$ One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone**

|                 |                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 8. Percentage of Subjects With Anti-pneumococcal Antigen Antibodies $\geq 0.35$ $\mu\text{g/mL}$ One Month After Toddler Vaccination With PCV Administered With MenACWY-CRM Compared With PCV Given Alone |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The immune response was measured as the percentage of subjects with anti-pneumococcal antigen antibodies  $\geq 0.35$   $\mu\text{g/mL}$  against pneumococcal antigens PnC 4, 6B, 9V, 14, 18C, 19F and 23F, one month after toddler dose of PCV at 12 months of age when administered concomitantly with MenACWY-CRM compared with PCV given alone.

Analysis was performed on the PP pneumococcal toddler population.

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

End point timeframe:

One month after PCV toddler vaccination

| End point values                 | MenACWY-CRM<br>+ Routine<br>Vaccines | Routine<br>Vaccines |  |  |
|----------------------------------|--------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group     |  |  |
| Number of subjects analysed      | 161                                  | 170                 |  |  |
| Units: Percentage of subjects    |                                      |                     |  |  |
| number (confidence interval 95%) |                                      |                     |  |  |
| PnC 4                            | 93 (88 to 97)                        | 96 (92 to 98)       |  |  |
| PnC 6B                           | 99 (97 to 100)                       | 98 (95 to 100)      |  |  |
| PnC 9V                           | 97 (93 to 99)                        | 96 (92 to 98)       |  |  |
| PnC 14                           | 99 (96 to 100)                       | 99 (97 to 100)      |  |  |
| PnC 18C                          | 96 (92 to 99)                        | 98 (94 to 99)       |  |  |
| PnC 19F (N=161,169)              | 99 (96 to 100)                       | 100 (98 to 100)     |  |  |
| PnC 23F                          | 99 (97 to 100)                       | 98 (94 to 99)       |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 9. Antibody Persistence by Percentage of Subjects With hSBA Titers $\geq 1:8$ Against Serogroup A, C, W and Y at 12 Months of Age Prior to Toddler

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 9. Antibody Persistence by Percentage of Subjects With hSBA Titers $\geq 1:8$ Against Serogroup A, C, W and Y at 12 Months of Age Prior to Toddler Vaccination |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The antibody persistence was measured as the percentage of subjects with hSBA titers  $\geq 1:8$  against meningococcal serogroup A, C, W and Y, at baseline and six months after three doses of infant series vaccination administered at 6 months (12 months of age), before administration of the toddler vaccination.

Analysis was performed on the PP toddler dataset for MenACWY-CRM.

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

End point timeframe:

Baseline and six months after three doses of infant series vaccination

| End point values                    | MenACWY-CRM<br>+ Routine<br>Vaccines | Routine<br>Vaccines |  |  |
|-------------------------------------|--------------------------------------|---------------------|--|--|
| Subject group type                  | Reporting group                      | Reporting group     |  |  |
| Number of subjects analysed         | 170                                  | 178                 |  |  |
| Units: Percentage of subjects       |                                      |                     |  |  |
| number (confidence interval 95%)    |                                      |                     |  |  |
| Serogroup A - Baseline (N=139, 145) | 1 (0 to 5)                           | 0 (0 to 3)          |  |  |

|                                              |               |              |  |  |
|----------------------------------------------|---------------|--------------|--|--|
| Serogroup A - 6 mo Post-3rd dose (N=168,175) | 7 (4 to 12)   | 2 (0 to 5)   |  |  |
| Serogroup C - Baseline (N=126,136)           | 7 (3 to 13)   | 8 (4 to 14)  |  |  |
| Serogroup C - 6 mo Post-3rd dose (N=156,171) | 37 (30 to 45) | 2 (1 to 6)   |  |  |
| Serogroup W - Baseline (N=113,126)           | 15 (9 to 23)  | 15 (9 to 23) |  |  |
| Serogroup W - 6 mo Post-3rd dose (N=153,165) | 70 (62 to 77) | 5 (2 to 9)   |  |  |
| Serogroup Y - Baseline (N=108,113)           | 6 (3 to 13)   | 5 (2 to 11)  |  |  |
| Serogroup Y - 6 mo Post-3rd dose (N=153,159) | 53 (45 to 61) | 3 (1 to 6)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: 10. Persistence of hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y, at 12 Months of Age, Prior to Toddler Vaccination

|                 |                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 10. Persistence of hSBA Geometric Mean Titers (GMTs) Against Serogroup A, C, W and Y, at 12 Months of Age, Prior to Toddler Vaccination |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The antibody persistence was measured as the hSBA GMTs directed against meningococcal serogroup A, C, W and Y, at baseline and six months after third infant vaccination administered at 6 months (12 months of age), before administration of the toddler dose vaccination.

Analysis was performed on the PP toddler dataset for MenACWY-CRM.

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

End point timeframe:

Baseline and six months after three doses of infant series vaccination

| End point values                             | MenACWY-CRM + Routine Vaccines | Routine Vaccines    |  |  |
|----------------------------------------------|--------------------------------|---------------------|--|--|
| Subject group type                           | Reporting group                | Reporting group     |  |  |
| Number of subjects analysed                  | 170                            | 178                 |  |  |
| Units: Titers                                |                                |                     |  |  |
| geometric mean (confidence interval 95%)     |                                |                     |  |  |
| Serogroup A - Baseline (N=139, 145)          | 2.07 (1.98 to 2.16)            | 2.01 (1.99 to 2.03) |  |  |
| Serogroup A - 6 mo Post-3rd dose (N=168,175) | 2.52 (2.26 to 2.82)            | 2.12 (2 to 2.25)    |  |  |
| Serogroup C - Baseline (N=126,136)           | 2.49 (2.2 to 2.83)             | 2.44 (2.2 to 2.7)   |  |  |
| Serogroup C - 6 mo Post-3rd dose (N=156,171) | 5.98 (4.81 to 7.43)            | 2.15 (2.02 to 2.3)  |  |  |
| Serogroup W - Baseline (N=113,126)           | 2.99 (2.49 to 3.6)             | 2.97 (2.52 to 3.51) |  |  |
| Serogroup W - 6 mo Post-3rd dose (N=153,165) | 15 (12 to 18)                  | 2.23 (2.06 to 2.4)  |  |  |
| Serogroup Y - Baseline (N=108,113)           | 2.43 (2.19 to 2.71)            | 2.32 (2.13 to 2.52) |  |  |

|                                                 |                  |                  |  |  |
|-------------------------------------------------|------------------|------------------|--|--|
| Serogroup Y - 6 mo Post-3rd dose<br>(N=153,159) | 8.39 (6.9 to 10) | 2.09 (2 to 2.19) |  |  |
|-------------------------------------------------|------------------|------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: 11. Percentage of Subjects With Four-fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Toddler Vaccination

|                 |                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| End point title | 11. Percentage of Subjects With Four-fold Increase in hSBA Titers Against Serogroup A, C, W and Y One Month After Toddler Vaccination |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The immune response was measured as the percentage of subjects who achieved four-fold increase in hSBA titers against meningococcal serogroup A, C, W and Y one month after toddler vaccination administered at 12 months of age (compared to hSBA at Month 12, just before toddler dose). Analysis was performed on the PP toddler dataset for MenACWY-CRM.

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

End point timeframe:

One month after toddler vaccination (month 13)

| End point values                 | MenACWY-CRM<br>+ Routine<br>Vaccines | Routine<br>Vaccines |  |  |
|----------------------------------|--------------------------------------|---------------------|--|--|
| Subject group type               | Reporting group                      | Reporting group     |  |  |
| Number of subjects analysed      | 168                                  | 175                 |  |  |
| Units: Percentage of subjects    |                                      |                     |  |  |
| number (confidence interval 95%) |                                      |                     |  |  |
| Serogroup A (N=168,175)          | 89 (83 to 93)                        | 1 (0.014 to 3)      |  |  |
| Serogroup C (N=156,171)          | 92 (87 to 96)                        | 1 (0 to 4)          |  |  |
| Serogroup W (N=153,165)          | 95 (91 to 98)                        | 2 (1 to 6)          |  |  |
| Serogroup Y (N=153,159)          | 96 (92 to 99)                        | 1 (0.016 to 3)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: 12. Safety of MenACWY-CRM Vaccinations When Administered Concomitantly With Routine Vaccinations

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | 12. Safety of MenACWY-CRM Vaccinations When Administered Concomitantly With Routine Vaccinations |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

Safety of the study vaccines (MenACWY-CRM and other routine vaccines) was assessed in terms of the number of subjects who reported adverse events (AEs) and/or serious AEs per vaccine group at the following time points: entire study period, after infants vaccination (up to 7 months), between 2- and 4-months, between 4- and 6-months, between 6- and 12-months, between 7- and 12-months, 28 days



after 12-month vaccination, and between 29 days after 12-month vaccination and study termination. Solicited reactions were not collected during this study. The safety analyses also included any AEs observed by study personnel within 15 minutes following vaccination. All AEs and SAEs were judged by the investigator as probably related, possibly related, or not related to vaccine. Analysis was done on Safety Set, i.e. all subjects in the exposed population who provide post-baseline safety data.

|                                                                   |           |
|-------------------------------------------------------------------|-----------|
| End point type                                                    | Secondary |
| End point timeframe:                                              |           |
| From visit 1 (2 months of age) through visit 7 (18 months of age) |           |

| End point values                                   | MenACWY-CRM + Routine Vaccines | Routine Vaccines |  |  |
|----------------------------------------------------|--------------------------------|------------------|--|--|
| Subject group type                                 | Reporting group                | Reporting group  |  |  |
| Number of subjects analysed                        | 255                            | 270              |  |  |
| Units: Percentage of subjects                      |                                |                  |  |  |
| number (not applicable)                            |                                |                  |  |  |
| Entire study - Any AEs                             | 228                            | 239              |  |  |
| Entire study - At least possibly related AEs       | 6                              | 2                |  |  |
| Entire study - Serious AEs                         | 21                             | 20               |  |  |
| Up to 7 months - Any AEs                           | 183                            | 189              |  |  |
| Up to 7 months - At least possibly related AEs     | 6                              | 1                |  |  |
| Up to 7 months - Serious AEs                       | 7                              | 8                |  |  |
| Between 2- and 4-months - Any AEs                  | 99                             | 105              |  |  |
| Between 2- & 4-mo - At least possibly related AEs  | 1                              | 0                |  |  |
| Between 2- and 4-months - Serious AEs              | 5                              | 5                |  |  |
| Between 4- and 6-months - Any AEs                  | 118                            | 114              |  |  |
| Between 4- & 6-mo - At least possibly related AEs  | 3                              | 0                |  |  |
| Between 4- and 6-months - Serious AEs              | 2                              | 2                |  |  |
| Between 6- and 12-months - Any AEs                 | 187                            | 197              |  |  |
| Between 6- & 12-mo - At least possibly related AEs | 2                              | 1                |  |  |
| Between 6- and 12-months - Serious AEs             | 10                             | 2                |  |  |
| Between 7- and 12-months - Any AEs                 | 175                            | 181              |  |  |
| Between 7- & 12-mo - At least possibly related AEs | 0                              | 0                |  |  |
| Between 7- and 12-months - Serious AEs             | 9                              | 2                |  |  |
| 28 days post-toddler - Any AEs                     | 80                             | 78               |  |  |
| 28 days post-toddler-At least possibly related AEs | 0                              | 0                |  |  |
| 28 days post-toddler - Serious AEs                 | 1                              | 1                |  |  |
| Between 29 days and study termination - Any AEs    | 137                            | 137              |  |  |
| B/w 29 days & study terminat-Possibly related AEs  | 0                              | 0                |  |  |
| Between 29 days and study termination - SeriousAEs | 7                              | 11               |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from day 1 to 18 months

Adverse event reporting additional description:

The number of subjects reported here is from the safety set and not from the enrolled set.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Routine Vaccines |
|-----------------------|------------------|

Reporting group description:

Infants received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | MenACWY-CRM + Routine Vaccines |
|-----------------------|--------------------------------|

Reporting group description:

Infants received 3 doses of MenACWY-CRM at 2, 4 and 6 months as an infant series vaccination and a toddler dose at 12 months. Infants also received routine vaccines - 3 doses each of DTaP-IPV/Hib, HBV and PCV at 2, 4 and 6 months; and 1 dose each of PCV and MMR at 12 months.

| Serious adverse events                            | Routine Vaccines | MenACWY-CRM + Routine Vaccines |  |
|---------------------------------------------------|------------------|--------------------------------|--|
| Total subjects affected by serious adverse events |                  |                                |  |
| subjects affected / exposed                       | 20 / 270 (7.41%) | 21 / 255 (8.24%)               |  |
| number of deaths (all causes)                     | 0                | 0                              |  |
| number of deaths resulting from adverse events    | 0                | 0                              |  |
| Investigations                                    |                  |                                |  |
| Moraxella Test Positive                           |                  |                                |  |
| subjects affected / exposed                       | 0 / 270 (0.00%)  | 1 / 255 (0.39%)                |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1                          |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                          |  |
| Injury, poisoning and procedural complications    |                  |                                |  |
| Skull fracture                                    |                  |                                |  |
| subjects affected / exposed                       | 0 / 270 (0.00%)  | 1 / 255 (0.39%)                |  |
| occurrences causally related to treatment / all   | 0 / 0            | 0 / 1                          |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                          |  |
| Congenital, familial and genetic disorders        |                  |                                |  |
| Laryngomalacia                                    |                  |                                |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Surgical and medical procedures</b>          |                 |                 |  |
| Colectomy                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colostomy                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Nervous system disorders</b>                 |                 |                 |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cognitive Disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile Convulsion                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sensory disturbance                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal Motility Disorder              |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired Gastric Emptying                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Vaginal laceration                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Respiratory Distress                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchiolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess                                         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium Difficile Infection                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Croup Infectious                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 270 (1.11%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis Enteroviral                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metapneumovirus Infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis Media                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Parainfluenzae Viral                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Viral                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Syncytial Virus<br>Bronchiolitis    |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous Abscess                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tonsillitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral Infection                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary Tract Infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Failure To Thrive                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Routine Vaccines   | MenACWY-CRM + Routine Vaccines |  |
|-------------------------------------------------------|--------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events |                    |                                |  |
| subjects affected / exposed                           | 227 / 270 (84.07%) | 216 / 255 (84.71%)             |  |
| General disorders and administration site conditions  |                    |                                |  |
| Pyrexia                                               |                    |                                |  |
| subjects affected / exposed                           | 45 / 270 (16.67%)  | 43 / 255 (16.86%)              |  |
| occurrences (all)                                     | 58                 | 51                             |  |
| Gastrointestinal disorders                            |                    |                                |  |
| Constipation                                          |                    |                                |  |
| subjects affected / exposed                           | 24 / 270 (8.89%)   | 18 / 255 (7.06%)               |  |
| occurrences (all)                                     | 24                 | 18                             |  |
| Diarrhoea                                             |                    |                                |  |
| subjects affected / exposed                           | 26 / 270 (9.63%)   | 25 / 255 (9.80%)               |  |
| occurrences (all)                                     | 28                 | 25                             |  |
| Teething                                              |                    |                                |  |



|                                                                               |                         |                         |  |
|-------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                              | 7 / 270 (2.59%)<br>7    | 16 / 255 (6.27%)<br>18  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                  | 31 / 270 (11.48%)<br>33 | 19 / 255 (7.45%)<br>23  |  |
| Respiratory, thoracic and mediastinal disorders                               |                         |                         |  |
| Bronchial hyperreactivity<br>subjects affected / exposed<br>occurrences (all) | 8 / 270 (2.96%)<br>9    | 15 / 255 (5.88%)<br>15  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                     | 27 / 270 (10.00%)<br>34 | 34 / 255 (13.33%)<br>51 |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)         | 21 / 270 (7.78%)<br>31  | 17 / 255 (6.67%)<br>33  |  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)                  | 8 / 270 (2.96%)<br>8    | 16 / 255 (6.27%)<br>18  |  |
| Skin and subcutaneous tissue disorders                                        |                         |                         |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)                    | 28 / 270 (10.37%)<br>30 | 29 / 255 (11.37%)<br>29 |  |
| Dermatitis atopic<br>subjects affected / exposed<br>occurrences (all)         | 17 / 270 (6.30%)<br>18  | 17 / 255 (6.67%)<br>18  |  |
| Dermatitis diaper<br>subjects affected / exposed<br>occurrences (all)         | 40 / 270 (14.81%)<br>47 | 33 / 255 (12.94%)<br>46 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                      | 15 / 270 (5.56%)<br>17  | 13 / 255 (5.10%)<br>13  |  |
| Infections and infestations                                                   |                         |                         |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)            | 55 / 270 (20.37%)<br>74 | 60 / 255 (23.53%)<br>63 |  |
| Bronchitis                                                                    |                         |                         |  |

|                                   |                    |                    |
|-----------------------------------|--------------------|--------------------|
| subjects affected / exposed       | 15 / 270 (5.56%)   | 15 / 255 (5.88%)   |
| occurrences (all)                 | 16                 | 17                 |
| Bronchiolitis                     |                    |                    |
| subjects affected / exposed       | 40 / 270 (14.81%)  | 37 / 255 (14.51%)  |
| occurrences (all)                 | 50                 | 44                 |
| Candida nappy rash                |                    |                    |
| subjects affected / exposed       | 17 / 270 (6.30%)   | 6 / 255 (2.35%)    |
| occurrences (all)                 | 19                 | 6                  |
| Candida infection                 |                    |                    |
| subjects affected / exposed       | 24 / 270 (8.89%)   | 16 / 255 (6.27%)   |
| occurrences (all)                 | 28                 | 21                 |
| Croup infectious                  |                    |                    |
| subjects affected / exposed       | 21 / 270 (7.78%)   | 15 / 255 (5.88%)   |
| occurrences (all)                 | 22                 | 16                 |
| Otitis media                      |                    |                    |
| subjects affected / exposed       | 101 / 270 (37.41%) | 100 / 255 (39.22%) |
| occurrences (all)                 | 226                | 249                |
| Gastroenteritis                   |                    |                    |
| subjects affected / exposed       | 32 / 270 (11.85%)  | 38 / 255 (14.90%)  |
| occurrences (all)                 | 37                 | 44                 |
| Otitis media acute                |                    |                    |
| subjects affected / exposed       | 31 / 270 (11.48%)  | 31 / 255 (12.16%)  |
| occurrences (all)                 | 50                 | 46                 |
| Pharyngitis                       |                    |                    |
| subjects affected / exposed       | 32 / 270 (11.85%)  | 24 / 255 (9.41%)   |
| occurrences (all)                 | 43                 | 27                 |
| Rhinitis                          |                    |                    |
| subjects affected / exposed       | 20 / 270 (7.41%)   | 19 / 255 (7.45%)   |
| occurrences (all)                 | 20                 | 19                 |
| Sinusitis                         |                    |                    |
| subjects affected / exposed       | 15 / 270 (5.56%)   | 10 / 255 (3.92%)   |
| occurrences (all)                 | 15                 | 21                 |
| Upper respiratory tract infection |                    |                    |
| subjects affected / exposed       | 154 / 270 (57.04%) | 144 / 255 (56.47%) |
| occurrences (all)                 | 321                | 300                |
| Viral infection                   |                    |                    |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 51 / 270 (18.89%) | 36 / 255 (14.12%) |  |
| occurrences (all)           | 58                | 49                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 November 2009 | - The subjects in Group 2, the Control group will be administered one dose of MenACWY at Visit 7 with one month of follow up. This will extend the study period by 1 month, from 16 months to 17 months. |
| 21 January 2010  | - Need to clarify what vaccines can be administered and when they should be administered.<br>- Need to clarify where injection should be given.                                                          |
| 29 July 2011     | - The protocol is being amended to reflect changes to the primary and secondary endpoints, and to describe the switch from Pre-Filled Syringe (PFS) to vial-vial presentation.                           |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported