



## Clinical trial results:

### A Phase IIIb, Open-Label, Controlled, Multi-Center Study to Evaluate the Persistence Of Antibody Responses Among Children Who Previously Received Novartis MenACWY Conjugate Vaccine or Meningococcal C Conjugate Vaccine

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2010-023858-37    |
| Trial protocol           | DE                |
| Global end of trial date | 08 September 2011 |

#### Results information

|                                |                                                                                                             |
|--------------------------------|-------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                |
| This version publication date  | 11 May 2016                                                                                                 |
| First version publication date | 28 December 2014                                                                                            |
| Version creation reason        | <ul style="list-style-type: none"><li>Correction of full data set</li></ul> Data points need to be updated. |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | V59P22E1 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01345721 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                       |
|------------------------------|-------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Vaccines and Diagnostics S.r.l.                                                              |
| Sponsor organisation address | Via Fiorentina, 1, Siena, Italy, 53100                                                                |
| Public contact               | Posting Director, Novartis Vaccines and Diagnostics S.r.l.,<br>RegistryContactVaccinesUS@novartis.com |
| Scientific contact           | Posting Director, Novartis Vaccines and Diagnostics S.r.l.,<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                       | 03 May 2012       |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 08 September 2011 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

Co-primary objectives:

- 1.To evaluate the persistence of the antibody response in children previously vaccinated with one or two doses of MenACWY or MenC in study V59P22, as measured by percentage of subjects with human Serum Bactericidal Assay (hSBA) titers  $\geq 1:8$  directed against N. meningitidis serogroups A, C, W and Y.
- 2.To evaluate the antibody response to a booster dose of MenACWY in children previously vaccinated with one or two doses of MenACWY as measured by of percentage of subjects with hSBA titers  $\geq 1:8$ , and hSBA GMTs directed against N.meningitidis serogroups A, C, W, Y.
- 3.To evaluate the antibody response to one dose of MenACWY in children previously vaccinated with MenC as measured by of percentage of subjects with hSBA titers  $\geq 1:8$ , and hSBA GMTs directed against N. meningitidis serogroups A, C, W, Y.

Protection of trial subjects:

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

Background therapy:

MenACWY

Evidence for comparator:

MenC

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 25 May 2011 |
| 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 | Germany: 205 |
| Worldwide total number of subjects   | 205          |
| EEA total number of subjects         | 205          |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 205 |
| 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 for this extension study were enrolled between 25 May 2011 and 08 September 2011 from only sites in Germany that participated in the parent study.

### Pre-assignment

Screening details:

Subjects were 22 to 45 months of age at the time of enrolment into V59P22E1 and had participated in the original V59P22 study.

### Period 1

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

### Arms

|                              |                                   |
|------------------------------|-----------------------------------|
| Are arms mutually exclusive? | Yes                               |
| <b>Arm title</b>             | MenACWY_2 doses + MenACWY booster |

Arm description:

Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

|                                        |                                                                                                          |
|----------------------------------------|----------------------------------------------------------------------------------------------------------|
| Arm type                               | Experimental                                                                                             |
| Investigational medicinal product name | MenACWY-CRM                                                                                              |
| Investigational medicinal product code |                                                                                                          |
| Other name                             | Meningococcal (groups A, C, Y, and W-135 vaccine)<br>Oligosaccharide Diphtheria-CRM197 Conjugate Vaccine |
| Pharmaceutical forms                   | Powder and solution for solution for injection                                                           |
| Routes of administration               | Intramuscular use                                                                                        |

Dosage and administration details:

MenACWY was obtained by extemporaneous mixing just before injection of the lyophilized MenA component with the liquid MenCWY component. One 0.5 mL dose of MenACWY was administered by IM injection in the left deltoid.

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | MenACWY_1 dose + MenACWY booster |
|------------------|----------------------------------|

Arm description:

Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

|                                        |                                                                                                          |
|----------------------------------------|----------------------------------------------------------------------------------------------------------|
| Arm type                               | Experimental                                                                                             |
| Investigational medicinal product name | MenACWY-CRM                                                                                              |
| Investigational medicinal product code |                                                                                                          |
| Other name                             | Meningococcal (groups A, C, Y, and W-135 vaccine)<br>Oligosaccharide Diphtheria-CRM197 Conjugate Vaccine |
| Pharmaceutical forms                   | Powder and solution for solution for injection                                                           |
| Routes of administration               | Intramuscular use                                                                                        |

Dosage and administration details:

MenACWY was obtained by extemporaneous mixing just before injection of the lyophilized MenA component with the liquid MenCWY component. One 0.5 mL dose of MenACWY was administered by IM injection in the left deltoid.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Men C + MenACWY booster |
|------------------|-------------------------|

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**Arm description:**

Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.

|                                        |                                                |
|----------------------------------------|------------------------------------------------|
| Arm type                               | Experimental                                   |
| Investigational medicinal product name | MenACWY-CRM                                    |
| Investigational medicinal product code |                                                |
| Other name                             |                                                |
| Pharmaceutical forms                   | Powder and solution for solution for injection |
| Routes of administration               | Intramuscular use                              |

**Dosage and administration details:**

MenACWY was obtained by extemporaneous mixing just before injection of the lyophilized MenA component with the liquid MenCWY component. One 0.5 mL dose of MenACWY was administered by IM injection in the left deltoid.

| <b>Number of subjects in period 1</b> | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |
|---------------------------------------|-----------------------------------|----------------------------------|-------------------------|
| Started                               | 74                                | 66                               | 65                      |
| Completed                             | 74                                | 66                               | 65                      |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                              |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                        | MenACWY_2 doses + MenACWY booster |
| Reporting group description:<br>Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.  |                                   |
| Reporting group title                                                                                                                                                                                                                        | MenACWY_1 dose + MenACWY booster  |
| Reporting group description:<br>Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.                     |                                   |
| Reporting group title                                                                                                                                                                                                                        | Men C + MenACWY booster           |
| Reporting group description:<br>Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study. |                                   |

| Reporting group values                | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |
|---------------------------------------|-----------------------------------|----------------------------------|-------------------------|
| Number of subjects                    | 74                                | 66                               | 65                      |
| Age categorical<br>Units: Subjects    |                                   |                                  |                         |
| Children (2-11 years)                 | 74                                | 66                               | 65                      |
| Age continuous<br>Units: months       |                                   |                                  |                         |
| arithmetic mean                       | 36.7                              | 37.4                             | 37.9                    |
| standard deviation                    | ± 5.3                             | ± 5.6                            | ± 5.3                   |
| Gender categorical<br>Units: Subjects |                                   |                                  |                         |
| Female                                | 34                                | 30                               | 37                      |
| Male                                  | 40                                | 36                               | 28                      |

| Reporting group values                | Total |  |  |
|---------------------------------------|-------|--|--|
| Number of subjects                    | 205   |  |  |
| Age categorical<br>Units: Subjects    |       |  |  |
| Children (2-11 years)                 | 205   |  |  |
| Age continuous<br>Units: months       |       |  |  |
| arithmetic mean                       | -     |  |  |
| standard deviation                    | -     |  |  |
| Gender categorical<br>Units: Subjects |       |  |  |
| Female                                | 101   |  |  |
| Male                                  | 104   |  |  |

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**Subject analysis sets**

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Per Protocol Persistence Population |
| Subject analysis set type  | Per protocol                        |

Subject analysis set description:

All subjects who provided evaluable serum samples at visit 7 and had no major protocol violation as defined prior to the end of the study

|                            |                   |
|----------------------------|-------------------|
| Subject analysis set title | Safety Population |
| Subject analysis set type  | Safety analysis   |

Subject analysis set description:

All subjects in the Exposed population who received at least one dose of study vaccine, and provided some post-vaccination safety data

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Per-protocol Population |
| Subject analysis set type  | Per protocol            |

Subject analysis set description:

All enrolled subjects who correctly received the vaccine, provided evaluable serum samples at the relevant time points (Day 28), and had no major protocol violation as defined prior to the end of the study.

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| Reporting group values                                                   | Per Protocol Persistence Population | Safety Population | Per-protocol Population |
|--------------------------------------------------------------------------|-------------------------------------|-------------------|-------------------------|
| Number of subjects                                                       | 136                                 | 140               | 134                     |
| Age categorical<br>Units: Subjects                                       |                                     |                   |                         |
| Children (2-11 years)                                                    | 136                                 | 140               | 134                     |
| Age continuous<br>Units: months<br>arithmetic mean<br>standard deviation | ±                                   | ±                 | ±                       |
| Gender categorical<br>Units: Subjects                                    |                                     |                   |                         |
| Female<br>Male                                                           |                                     |                   |                         |

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## End points

### End points reporting groups

|                                                                                                                                                                                                                                                     |                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Reporting group title                                                                                                                                                                                                                               | MenACWY_2 doses + MenACWY booster   |
| Reporting group description:<br>Subjects, who had received two doses of MenACWY (at 6 to 8 months and 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.         |                                     |
| Reporting group title                                                                                                                                                                                                                               | MenACWY_1 dose + MenACWY booster    |
| Reporting group description:<br>Subjects, who had received one dose of MenACWY (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.                            |                                     |
| Reporting group title                                                                                                                                                                                                                               | Men C + MenACWY booster             |
| Reporting group description:<br>Subjects, who had received one dose of the comparator MenC vaccine (at 12 months of age) in the parent study, were administered a booster dose of MenACWY at 22 to 45 months of age in this extension study.        |                                     |
| Subject analysis set title                                                                                                                                                                                                                          | Per Protocol Persistence Population |
| Subject analysis set type                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All subjects who provided evaluable serum samples at visit 7 and had no major protocol violation as defined prior to the end of the study                                                                      |                                     |
| Subject analysis set title                                                                                                                                                                                                                          | Safety Population                   |
| Subject analysis set type                                                                                                                                                                                                                           | Safety analysis                     |
| Subject analysis set description:<br>All subjects in the Exposed population who received at least one dose of study vaccine, and provided some post-vaccination safety data                                                                         |                                     |
| Subject analysis set title                                                                                                                                                                                                                          | Per-protocol Population             |
| Subject analysis set type                                                                                                                                                                                                                           | Per protocol                        |
| Subject analysis set description:<br>All enrolled subjects who correctly received the vaccine, provided evaluable serum samples at the relevant time points (Day 28), and had no major protocol violation as defined prior to the end of the study. |                                     |

### Primary: Percentage of Subjects With Persisting Serum Bactericidal Antibody Titers $\geq 1:8$ , Upto 13-33 Months After Primary Vaccination With Either MenACWY-CRM or MenC Vaccine

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Percentage of Subjects With Persisting Serum Bactericidal Antibody Titers $\geq 1:8$ , Upto 13-33 Months After Primary Vaccination With Either MenACWY-CRM or MenC Vaccine <sup>[1]</sup> |
| End point description:<br>The percentage of subjects with persisting serum bactericidal antibody (hSBA) titers $\geq 1:8$ against <i>Neisseria meningitidis</i> serogroups A,C,W,Y, 13-33 months after receiving either one or two doses of MenACWY-CRM conjugate vaccine or one dose of MenC vaccine in parent study, is reported. The functional bactericidal antibodies response against <i>N. meningitidis</i> serogroups was measured with the serum bactericidal assay using human complement (hSBA).<br>The analysis was done on the per-protocol persistence population. |                                                                                                                                                                                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Primary                                                                                                                                                                                   |
| End point timeframe:<br>13-33 months post-primary vaccination                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                           |

#### Notes:

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

Justification: No statistical analyses were associated with this end point

| End point values                                   | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |
|----------------------------------------------------|-----------------------------------|----------------------------------|-------------------------|--|
| Subject group type                                 | Reporting group                   | Reporting group                  | Reporting group         |  |
| Number of subjects analysed                        | 52                                | 41                               | 43                      |  |
| Units: Percentage of Subjects                      |                                   |                                  |                         |  |
| number (confidence interval 95%)                   |                                   |                                  |                         |  |
| 13-33 months persistence (Serogroup A)             | 13 (6 to 26)                      | 7 (2 to 20)                      | 0 (0 to 8)              |  |
| 13-33 months persistence (Serogroup C)(N=52,40,42) | 27 (16 to 41)                     | 25 (13 to 41)                    | 36 (22 to 52)           |  |
| 13-33 months persistence (Serogroup W-135)         | 50 (36 to 64)                     | 63 (47 to 78)                    | 12 (4 to 25)            |  |
| 13-33 months persistence (Serogroup Y)             | 40 (27 to 55)                     | 39 (24 to 55)                    | 19 (8 to 33)            |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects With Serum Bactericidal Antibody Titers $\geq 1:8$ , One Month After MenACWY-CRM Booster Vaccination

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Serum Bactericidal Antibody Titers $\geq 1:8$ , One Month After MenACWY-CRM Booster Vaccination <sup>[2][3]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The serum antibody response following a booster dose of MenACWY-CRM conjugate vaccine in children, who had previously received either one or two doses of the same vaccine in the parent study, is reported as percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups A,C,W,Y. The analysis was performed on the per-protocol population.

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

End point timeframe:

1 month post-booster vaccination

Notes:

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

Justification: No statistical analyses were associated with this end point

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

Justification: As per the objective [MenACWY\_2 doses + MenACWY booster] and [MenACWY\_1 dose + MenACWY booster] groups were analysed for this outcome measure.

| End point values                           | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster |  |  |
|--------------------------------------------|-----------------------------------|----------------------------------|--|--|
| Subject group type                         | Reporting group                   | Reporting group                  |  |  |
| Number of subjects analysed                | 52                                | 41                               |  |  |
| Units: Percentage of Subjects              |                                   |                                  |  |  |
| number (confidence interval 95%)           |                                   |                                  |  |  |
| Pre-booster (Serogroup A)                  | 13 (6 to 26)                      | 7 (2 to 20)                      |  |  |
| 1 month post booster (Serogroup A)         | 96 (87 to 100)                    | 98 (87 to 100)                   |  |  |
| Pre-booster (Serogroup C) N=52,40          | 27 (16 to 41)                     | 25 (13 to 41)                    |  |  |
| 1 month post booster (Serogroup C) N=52,40 | 100 (93 to 100)                   | 100 (91 to 100)                  |  |  |

|                                        |                 |                 |  |  |
|----------------------------------------|-----------------|-----------------|--|--|
| Pre-booster (Serogroup W-135)          | 50 (36 to 64)   | 63 (47 to 78)   |  |  |
| 1 month post booster (Serogroup W-135) | 100 (93 to 100) | 100 (91 to 100) |  |  |
| Pre-booster (Serogroup Y)              | 40 (27 to 55)   | 39 (24 to 55)   |  |  |
| 1 month post booster (Serogroup Y)     | 100 (93 to 100) | 100 (91 to 100) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Geometric Mean Titers in Children, One Month After MenACWY-CRM Booster Vaccination

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Geometric Mean Titers in Children, One Month After MenACWY-CRM Booster Vaccination <sup>[4]</sup> <sup>[5]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

The serum antibody titers following a booster dose of MenACWY-CRM conjugate vaccine in children, who had previously received either one or two doses of the same vaccine in the parent study, are reported as geometric mean titers (GMTs) against *N. meningitidis* serogroups A,C, W,Y.

The analysis was performed on the per-protocol population.

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

End point timeframe:

1 month post-booster vaccination

Notes:

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

Justification: No statistical analyses were associated with this end point

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

Justification: As per the objective [MenACWY\_2 doses + MenACWY booster] and [MenACWY\_1 dose + MenACWY booster] groups were analysed for this outcome measure.

| End point values                           | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster |  |  |
|--------------------------------------------|-----------------------------------|----------------------------------|--|--|
| Subject group type                         | Reporting group                   | Reporting group                  |  |  |
| Number of subjects analysed                | 52                                | 41                               |  |  |
| Units: Titers                              |                                   |                                  |  |  |
| geometric mean (confidence interval 95%)   |                                   |                                  |  |  |
| Pre-booster (Serogroup A)                  | 2.82 (2.35 to 3.38)               | 2.52 (2.05 to 3.09)              |  |  |
| 1 month post booster (Serogroup A)         | 182 (118 to 281)                  | 214 (131 to 350)                 |  |  |
| Pre-booster (Serogroup C) N=52,40          | 3.92 (2.92 to 5.26)               | 3.91 (2.79 to 5.48)              |  |  |
| 1 month post booster (Serogroup C) N=52,40 | 541 (399 to 733)                  | 968 (682 to 1372)                |  |  |
| Pre-booster (Serogroup W-135)              | 9.37 (6.3 to 14)                  | 12 (7.51 to 18)                  |  |  |
| 1 month post booster (Serogroup W-135)     | 799 (564 to 1133)                 | 1267 (854 to 1879)               |  |  |
| Pre-booster (Serogroup Y)                  | 6.79 (4.86 to 9.5)                | 6.04 (4.13 to 8.82)              |  |  |

|                                    |                  |                   |  |  |
|------------------------------------|------------------|-------------------|--|--|
| 1 month post booster (Serogroup Y) | 650 (448 to 941) | 676 (444 to 1027) |  |  |
|------------------------------------|------------------|-------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Subjects (Who Had Previously Received MenC Vaccine) With Serum Bactericidal Antibody Titers $\geq 1:8$ , After One Dose of MenACWY-CRM Vaccination

|                 |                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects (Who Had Previously Received MenC Vaccine) With Serum Bactericidal Antibody Titers $\geq 1:8$ , After One Dose of MenACWY-CRM Vaccination <sup>[6][7]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The serum antibody response following a dose of MenACWY-CRM conjugate vaccine in children, who had previously received one dose of MenC vaccine in the parent study, is reported as percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups A,C, W,Y.

The analysis was performed on the per-protocol population.

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

End point timeframe:

1 month after vaccination

Notes:

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

Justification: No statistical analyses were associated with this end point

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

Justification: As per the objective [Men C + MenACWY booster] group was analysed for this outcome measure.

| End point values                            | Men C + MenACWY booster |  |  |  |
|---------------------------------------------|-------------------------|--|--|--|
| Subject group type                          | Reporting group         |  |  |  |
| Number of subjects analysed                 | 41                      |  |  |  |
| Units: Percentage of subjects               |                         |  |  |  |
| number (confidence interval 95%)            |                         |  |  |  |
| Prevaccination (Serogroup A)                | 0 (0 to 9)              |  |  |  |
| 1 month post vaccination (Serogroup A)      | 61 (45 to 76)           |  |  |  |
| Prevaccination (Serogroup C) N=39           | 36 (21 to 53)           |  |  |  |
| 1 month post vaccination (Serogroup C) N=39 | 100 (91 to 100)         |  |  |  |
| Pre-booster (Serogroup W-135)               | 12 (4 to 26)            |  |  |  |
| 1 month post vaccination (Serogroup W-135)  | 95 (83 to 99)           |  |  |  |
| Pre- vaccination (Serogroup Y)              | 20 (9 to 35)            |  |  |  |
| 1 month post vaccination (Serogroup Y)      | 95 (83 to 99)           |  |  |  |

## Statistical analyses

**Primary: Geometric Mean Titers in Children (Who Previously Received MenC Vaccine) One Month After One Dose of MenACWY-CRM Vaccine**

|                 |                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Geometric Mean Titers in Children (Who Previously Received MenC Vaccine) One Month After One Dose of MenACWY-CRM Vaccine <sup>[8][9]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

The serum antibody titers following one dose of MenACWY-CRM conjugate vaccine in children, who had previously received one dose of MenC vaccine in the parent study, are reported as GMTs against N. meningitidis serogroups A,C,W,Y.

The analysis was performed on the per-protocol population.

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

## End point timeframe:

1 month post vaccination

## Notes:

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

Justification: No statistical analyses were associated with this end point

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

Justification: As per the objective [Men C + MenACWY booster] group was analysed for this outcome measure.

| End point values                            | Men C + MenACWY booster |  |  |  |
|---------------------------------------------|-------------------------|--|--|--|
| Subject group type                          | Reporting group         |  |  |  |
| Number of subjects analysed                 | 41                      |  |  |  |
| Units: Titers                               |                         |  |  |  |
| geometric mean (confidence interval 95%)    |                         |  |  |  |
| Prevaccination (Serogroup A)                | 2 (1.63 to 2.45)        |  |  |  |
| 1 month post vaccination (Serogroup A)      | 20 (12 to 32)           |  |  |  |
| Prevaccination (Serogroup C) N=39           | 4.83 (3.44 to 6.77)     |  |  |  |
| 1 month post vaccination (Serogroup C) N=39 | 1530 (1077 to 2173)     |  |  |  |
| Pre-booster (Serogroup W-135)               | 2.82 (1.81 to 4.39)     |  |  |  |
| 1 month post vaccination (Serogroup W-135)  | 54 (37 to 80)           |  |  |  |
| Pre- vaccination (Serogroup Y)              | 3.05 (2.09 to 4.44)     |  |  |  |
| 1 month post vaccination (Serogroup Y)      | 54 (35 to 81)           |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of Children Reporting Solicited Local and Systemic Adverse Events (AEs) After MenACWY-CRM Vaccination**

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Number of Children Reporting Solicited Local and Systemic Adverse Events (AEs) After MenACWY-CRM Vaccination |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

The safety of MenACWY-CRM vaccine in children (who had previously received either one or two doses of MenACWY-CRM vaccine or one dose of MenC vaccine in the parent study) is assessed in terms of number of subjects reporting any unsolicited AEs (day 1 to day 7); serious AEs and AEs necessitating medical attention/or premature withdrawal (day 1 to day 28) after MenACWY-CRM vaccine. The analysis was performed on the safety population.

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

End point timeframe:

Day 1 to 7 after vaccination

| End point values                                        | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |
|---------------------------------------------------------|-----------------------------------|----------------------------------|-------------------------|--|
| Subject group type                                      | Reporting group                   | Reporting group                  | Reporting group         |  |
| Number of subjects analysed                             | 53                                | 44                               | 43                      |  |
| Units: Subjects                                         |                                   |                                  |                         |  |
| Any Solicited Local                                     | 33                                | 30                               | 30                      |  |
| Pain                                                    | 10                                | 15                               | 13                      |  |
| Erythema                                                | 14                                | 17                               | 15                      |  |
| Induration                                              | 6                                 | 8                                | 7                       |  |
| Any Solicited Systemic                                  | 28                                | 18                               | 25                      |  |
| Arthralgia                                              | 1                                 | 5                                | 4                       |  |
| Headache                                                | 5                                 | 6                                | 1                       |  |
| Vomiting                                                | 0                                 | 2                                | 1                       |  |
| Change in Eating Habits                                 | 6                                 | 8                                | 6                       |  |
| Rash                                                    | 0                                 | 2                                | 1                       |  |
| Sleepiness                                              | 10                                | 13                               | 10                      |  |
| Fever                                                   | 8                                 | 7                                | 7                       |  |
| Any other                                               | 5                                 | 7                                | 5                       |  |
| Stayed at home                                          | 4                                 | 5                                | 2                       |  |
| Analgesic Antipyretic Medication Used                   | 4                                 | 6                                | 5                       |  |
| Temperature ( $\geq 40^{\circ}\text{C}$ ) (N= 52,41,41) | 0                                 | 0                                | 2                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Persisting Geometric Mean Titers in Children, 13-33 Months After Primary Vaccination With Either MenACWY-CRM or MenC Vaccine

|                 |                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Persisting Geometric Mean Titers in Children, 13-33 Months After Primary Vaccination With Either MenACWY-CRM or MenC Vaccine |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

End point description:

The persisting serum bactericidal antibody titers in children, 13-33 months after receiving either one or two doses of MenACWY-CRM vaccine or one dose of Men C vaccine in the parent study, are reported as GMTs against N. meningitidis serogroups A,C, W,Y.

The analysis was performed on the per-protocol persistence population.

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

End point timeframe:

13-33 months after primary vaccination

| End point values                                | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |
|-------------------------------------------------|-----------------------------------|----------------------------------|-------------------------|--|
| Subject group type                              | Reporting group                   | Reporting group                  | Reporting group         |  |
| Number of subjects analysed                     | 52                                | 41                               | 43                      |  |
| Units: Titers                                   |                                   |                                  |                         |  |
| geometric mean (confidence interval 95%)        |                                   |                                  |                         |  |
| 13-33 months persistence (Serogroup A)          | 2.82 (2.36 to 3.37)               | 2.52 (2.05 to 3.08)              | 2 (1.64 to 2.43)        |  |
| 13-33 months persistence (Serogroup C)(N=52,40) | 3.94 (2.92 to 5.3)                | 3.93 (2.79 to 5.53)              | 4.94 (3.55 to 6.86)     |  |
| 13-33 months persistence (Serogroup W-135)      | 9.36 (6.31 to 14)                 | 12 (7.53 to 18)                  | 2.81 (1.82 to 4.32)     |  |
| 13-33 months persistence (Serogroup Y)          | 6.79 (4.87 to 9.47)               | 6.03 (4.14 to 8.78)              | 2.99 (2.08 to 4.3)      |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Serum Bactericidal Titers $\geq 1:8$ , Who Previously Received 1 Primary Dose of Either MenACWY-CRM or Men C Vaccine

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Serum Bactericidal Titers $\geq 1:8$ , Who Previously Received 1 Primary Dose of Either MenACWY-CRM or Men C Vaccine <sup>[10]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Comparison of serum antibody responses following one dose of MenACWY-CRM conjugate vaccine in children, who had previously received either one dose of the same vaccine or one dose of Men C vaccine in the parent study, is reported as percentage of subjects with hSBA titers  $\geq 1:8$  against N. meningitidis serogroups A,C,W,Y.

The analysis was performed on the per-protocol population.

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

End point timeframe:

1 month post vaccination

Notes:

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

Justification: As per the objective [MenACWY\_1 dose + MenACWY booster] and [Men C + MenACWY booster] groups were analysed for this outcome measure.

| End point values                      | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |  |
|---------------------------------------|----------------------------------|-------------------------|--|--|
| Subject group type                    | Reporting group                  | Reporting group         |  |  |
| Number of subjects analysed           | 41                               | 41                      |  |  |
| Units: Percentage of subjects         |                                  |                         |  |  |
| number (confidence interval 95%)      |                                  |                         |  |  |
| hSBA $\geq 1:8$ (Serogroup A)         | 98 (87 to 100)                   | 61 (45 to 76)           |  |  |
| hSBA $\geq 1:8$ (Serogroup C) N=40,39 | 100 (91 to 100)                  | 100 (91 to 100)         |  |  |
| hSBA $\geq 1:8$ (Serogroup W- 135)    | 100 (91 to 100)                  | 95 (83 to 99)           |  |  |
| hSBA $\geq 1:8$ (Serogroup Y)         | 100 (91 to 100)                  | 95 (83 to 99)           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric Mean Titers Following One Dose of MenACWY-CRM Vaccine in Children Who Previously Received 1 Primary Dose of Either MenACWY-CRM or Men C Vaccine

|                 |                                                                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Geometric Mean Titers Following One Dose of MenACWY-CRM Vaccine in Children Who Previously Received 1 Primary Dose of Either MenACWY-CRM or Men C Vaccine <sup>[11]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Comparison of serum antibody titers following a one dose of MenACWY-CRM conjugate vaccine in children, who had previously received either one dose of the same vaccine or one dose of MenC vaccine in the parent study, are reported as GMTs against N. meningitidis serogroups A,C, W,Y. The analysis was performed on the per-protocol population.

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

End point timeframe:

1 month post vaccination

Notes:

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

Justification: As per the objective [MenACWY\_1 dose + MenACWY booster] and [Men C + MenACWY booster] groups were analysed for this outcome measure.

| End point values                               | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |  |
|------------------------------------------------|----------------------------------|-------------------------|--|--|
| Subject group type                             | Reporting group                  | Reporting group         |  |  |
| Number of subjects analysed                    | 41                               | 41                      |  |  |
| Units: Titers                                  |                                  |                         |  |  |
| geometric mean (confidence interval 95%)       |                                  |                         |  |  |
| 1 month post vaccination (Serogroup A)         | 214 (131 to 350)                 | 20 (12 to 32)           |  |  |
| 1 month post vaccination (Serogroup C) N=40,39 | 968 (682 to 1372)                | 1530 (1077 to 2173)     |  |  |

|                                            |                    |               |  |  |
|--------------------------------------------|--------------------|---------------|--|--|
| 1 month post vaccination (Serogroup W-135) | 1267 (854 to 1879) | 54 (37 to 80) |  |  |
| 1 month post vaccination (Serogroup Y)     | 676 (444 to 1027)  | 54 (35 to 81) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Children Reporting Unsolicited Adverse Events After MenACWY-CRM Vaccination

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Number of Children Reporting Unsolicited Adverse Events After MenACWY-CRM Vaccination |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

The safety of MenACWY-CRM vaccine in children (who had previously received either one or two doses of MenACWY-CRM vaccine or one dose of MenC vaccine in the parent study) is assessed in terms of number of subjects reporting any unsolicited AEs (day 1 to day 7); serious AEs and AEs necessitating medical attention/or premature withdrawal (day 1 to day 28) after MenACWY-CRM vaccine.

The analysis was performed on the safety population.

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

End point timeframe:

Day 1-28 after vaccination

| End point values                    | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |  |
|-------------------------------------|-----------------------------------|----------------------------------|-------------------------|--|
| Subject group type                  | Reporting group                   | Reporting group                  | Reporting group         |  |
| Number of subjects analysed         | 53                                | 44                               | 43                      |  |
| Units: Subjects                     |                                   |                                  |                         |  |
| Any AE                              | 11                                | 10                               | 9                       |  |
| At least possibly related AEs       | 0                                 | 2                                | 1                       |  |
| Serious AE                          | 0                                 | 0                                | 0                       |  |
| AEs leading to premature withdrawal | 0                                 | 0                                | 0                       |  |
| Deaths                              | 0                                 | 0                                | 0                       |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Solicited and unsolicited AEs were collected from Day 1-7 after vaccination. SAEs and AEs necessitating medical attention/premature withdrawal were collected from Day 1-28.

Adverse event reporting additional description:

Due to non-compliance with protocol, data from one site was excluded in the parent study and subsequently from this extension study. Thus the numbers of subjects analyzed for safety differ from enrolled population.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 14 |
|--------------------|----|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | MenACWY_2 doses + MenACWY booster |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects, who had previously received two primary doses of MenACWY-CRM vaccine (at 6-8 months and 12 months of age) in parent study, were administered one booster dose of the same vaccine in this extension study.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | MenACWY_1 dose + MenACWY booster |
|-----------------------|----------------------------------|

Reporting group description:

Subjects, who had previously received one primary dose of MenACWY-CRM vaccine (at 12 months of age) in parent study, were administered one booster dose of the same vaccine in this extension study.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Men C + MenACWY booster |
|-----------------------|-------------------------|

Reporting group description:

Subjects, who had previously received one primary dose of the comparator MenC vaccine (at 12 months of age) in parent study, were administered one booster dose MenACWY-CRM vaccine in this extension study.

| Serious adverse events                            | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |
|---------------------------------------------------|-----------------------------------|----------------------------------|-------------------------|
| Total subjects affected by serious adverse events |                                   |                                  |                         |
| subjects affected / exposed                       | 0 / 53 (0.00%)                    | 0 / 44 (0.00%)                   | 0 / 43 (0.00%)          |
| number of deaths (all causes)                     | 0                                 | 0                                | 0                       |
| number of deaths resulting from adverse events    | 0                                 | 0                                | 0                       |

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

| Non-serious adverse events                            | MenACWY_2 doses + MenACWY booster | MenACWY_1 dose + MenACWY booster | Men C + MenACWY booster |
|-------------------------------------------------------|-----------------------------------|----------------------------------|-------------------------|
| Total subjects affected by non-serious adverse events |                                   |                                  |                         |
| subjects affected / exposed                           | 33 / 53 (62.26%)                  | 31 / 44 (70.45%)                 | 30 / 43 (69.77%)        |
| Nervous system disorders                              |                                   |                                  |                         |

|                                                                                                                                                                      |                        |                        |                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Somnolence<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                         | 10 / 53 (18.87%)<br>11 | 13 / 44 (29.55%)<br>15 | 10 / 43 (23.26%)<br>10 |
| Headache<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                           | 5 / 53 (9.43%)<br>5    | 6 / 44 (13.64%)<br>6   | 1 / 43 (2.33%)<br>1    |
| General disorders and administration<br>site conditions<br>Pyrexia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 8 / 53 (15.09%)<br>11  | 8 / 44 (18.18%)<br>9   | 7 / 43 (16.28%)<br>10  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                                                                                                     | 12 / 53 (22.64%)<br>13 | 8 / 44 (18.18%)<br>9   | 14 / 43 (32.56%)<br>16 |
| Injection site erythema<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                            | 14 / 53 (26.42%)<br>14 | 17 / 44 (38.64%)<br>17 | 15 / 43 (34.88%)<br>15 |
| Injection site induration<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                          | 6 / 53 (11.32%)<br>6   | 8 / 44 (18.18%)<br>8   | 7 / 43 (16.28%)<br>7   |
| Injection site pain<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all)                                                | 10 / 53 (18.87%)<br>10 | 15 / 44 (34.09%)<br>16 | 13 / 43 (30.23%)<br>14 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                                          | 4 / 53 (7.55%)<br>6    | 2 / 44 (4.55%)<br>3    | 8 / 43 (18.60%)<br>9   |
| Psychiatric disorders<br>Eating disorder<br>alternative assessment type:<br>Systematic                                                                               |                        |                        |                        |

|                                                                                                                                                                 |                      |                       |                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                                                                                                | 6 / 53 (11.32%)<br>6 | 8 / 44 (18.18%)<br>10 | 6 / 43 (13.95%)<br>7 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 1 / 53 (1.89%)<br>1  | 5 / 44 (11.36%)<br>5  | 4 / 43 (9.30%)<br>6  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 site was excluded as not compliant with the protocol requirements for safety reporting,(65 subjects [21 subjects in MenACWY 2-dose group, 22 subjects in MEnACWY 1-dose group and 22 subjects in MenC 1-dose group]) |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes: