



Clinical trial results:

A Phase 3, Open-Label, Randomized, Multi-Center Study to Evaluate the Safety and Immunogenicity of ProQuad™ Vaccine When Administered Concomitantly with Novartis Meningococcal ACWY Conjugate Vaccine to Healthy Toddlers.

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

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-004694-16 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 26 October 2010 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 01 June 2016 |
| First version publication date | 06 February 2015 |
| Version creation reason | • Correction of full data set re-QC study because of EudraCT system glitch and updates to results are required. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | V59P21 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00626327 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Vaccines and Diagnostics Inc. |
| Sponsor organisation address | 350 Massachusetts Ave, Cambridge, United States, 02139 |
| Public contact | Posting Director, Novartis Vaccines and Diagnostics Inc., RegistryContactVaccinesUS@novartis.com |
| Scientific contact | Posting Director, Novartis Vaccines and Diagnostics Inc., RegistryContactVaccinesUS@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000032-PIP01-07 |
| 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 | 11 February 2011 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 October 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare the immune responses of ProQuad™ vaccine when administered with MenACWY vaccine to that of ProQuad™ vaccine alone to children 12 months of age, as measured by seroconversion rates to measles, mumps, and rubella, and seroprotection rates for varicella.
- To compare the immune responses of two doses of MenACWY given to children at 7 to 9 and 12 months of age, when either administered with ProQuad™ or given alone, as measured by percentage of subjects with serum bactericidal activity (hSBA) $\geq 1:8$ against N. meningitidis serogroups A, C, W-135, and Y.
- To assess the immunogenicity of two doses of MenACWY given to children at 7 to 9 and 12 months of age as measured by the percentage of subjects with hSBA $\geq 1:8$ against N. meningitidis serogroups A, C, W-135, and Y.

Protection of trial subjects:

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

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|------------------|
| Actual start date of recruitment | 27 February 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United States: 1630 |
| Worldwide total number of subjects | 1630 |
| EEA total number of subjects | 0 |

Notes:

| Subjects enrolled per age group | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1630 |
| 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 at 90 sites in US.

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 subjects' parents/legal guardians knew which vaccine was being administered. However, laboratory immunogenicity analyses were conducted in a blinded fashion with samples blinded to both group and visit.

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ACWY + MMRV |

Arm description:

Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | ProQuad™ |
| Investigational medicinal product code | |
| Other name | Measles, Mumps, Rubella and Varicella vaccine |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

One dose of 0.5mL

| | |
|--|--|
| Investigational medicinal product name | MenACWY |
| Investigational medicinal product code | |
| Other name | Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Two doses of 0.5mL each

| | |
|------------------|------|
| Arm title | ACWY |
|------------------|------|

Arm description:

Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | ProQuad™ |
| Investigational medicinal product code | |
| Other name | Measles, Mumps, Rubella and Varicella vaccine |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

| | |
|--|--|
| Dosage and administration details: | |
| One dose of 0.5mL | |
| Investigational medicinal product name | MenACWY |
| Investigational medicinal product code | |
| Other name | Meningococcal (groups A, C, W, and Y) oligosaccharide diphtheria CRM-197 conjugate vaccine |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| Two doses of 0.5mL each | |
| Arm title | MMRV |
| Arm description: | |
| Subjects in this group received 1 injection of MMRV vaccine at 12 months of age. | |
| Arm type | Experimental |
| Investigational medicinal product name | ProQuad™ |
| Investigational medicinal product code | |
| Other name | Measles, Mumps, Rubella and Varicella vaccine |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| One dose of 0.5mL | |

| Number of subjects in period 1 | ACWY + MMRV | ACWY | MMRV |
|---------------------------------------|-------------|------|------|
| Started | 504 | 510 | 616 |
| Completed | 426 | 422 | 557 |
| Not completed | 78 | 88 | 59 |
| Consent withdrawn by subject | 21 | 30 | 29 |
| Adverse event, non-fatal | 1 | - | - |
| Inappropriate enrolment | 4 | 3 | 5 |
| Lost to follow-up | 24 | 23 | 21 |
| Administrative reason | 2 | 6 | - |
| Protocol deviation | 26 | 26 | 4 |

Baseline characteristics

Reporting groups

| | |
|---|-------------|
| Reporting group title | ACWY + MMRV |
| Reporting group description: Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV. | |
| Reporting group title | ACWY |
| Reporting group description: Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months. | |
| Reporting group title | MMRV |
| Reporting group description: Subjects in this group received 1 injection of MMRV vaccine at 12 months of age. | |

| Reporting group values | ACWY + MMRV | ACWY | MMRV |
|------------------------------------|-------------|------|------|
| Number of subjects | 504 | 510 | 616 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|--------------|--------------|---------------|
| Age continuous Units: months arithmetic mean standard deviation | 8.5 ± 0.8 | 8.5 ± 0.8 | 12.1 ± 0.3 |
| Gender categorical Units: Subjects | | | |
| Female | 251 | 252 | 304 |
| Male | 253 | 258 | 312 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 1630 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-----|--|--|
| Age continuous Units: months arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 807 | | |
| Male | 823 | | |

Subject analysis sets

| | |
|---|--------------------|
| Subject analysis set title | Exposed Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All enrolled subjects who actually received a study vaccination. | |

| | |
|--|--|
| Subject analysis set title | Enrolled Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All subjects who signed an informed consent, undergone screening procedure and were randomized (Groups I and II only) or enrolled (Group III). | |
| Subject analysis set title | MMRV Per Protocol Population (PP - MMRV) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| All subjects who actually received one study vaccination correctly, provided evaluable serum samples at the relevant time points, were seronegative at baseline for any of the four antigens (MMRV analyses only), were included in the analysis of those antigens, and had no major protocol deviation as defined prior to unblinding. These subjects would have received either ProQuad™ or M-M-R™II + Varivax™. | |
| Subject analysis set title | MenACWY Per Protocol Population (PP - MenACWY) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| All subjects who actually received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, were included in the analysis of that antigen, and had no major protocol deviation as defined prior to unblinding. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All subjects in the Exposed Population who provided post-baseline safety data. | |

| Reporting group values | Exposed Population | Enrolled Population | MMRV Per Protocol Population (PP - MMRV) |
|------------------------------------|--------------------|---------------------|--|
| Number of subjects | 1603 | 1630 | 1318 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|--|--------------|---|
| Age continuous Units: months arithmetic mean standard deviation | | 9.8 ± 1.9 | ± |
| Gender categorical Units: Subjects | | | |
| Female | | 807 | |
| Male | | 823 | |

| Reporting group values | MenACWY Per Protocol Population (PP - MenACWY) | Safety Population | |
|------------------------------------|--|-------------------|--|
| Number of subjects | 1319 | 1597 | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|---|---|--|
| Age continuous Units: months arithmetic mean standard deviation | ± | ± | |
| Gender categorical Units: Subjects | | | |
| Female | | | |
| Male | | | |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | ACWY + MMRV |
| Reporting group description: Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV. | |
| Reporting group title | ACWY |
| Reporting group description: Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months. | |
| Reporting group title | MMRV |
| Reporting group description: Subjects in this group received 1 injection of MMRV vaccine at 12 months of age. | |
| Subject analysis set title | Exposed Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All enrolled subjects who actually received a study vaccination. | |
| Subject analysis set title | Enrolled Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects who signed an informed consent, undergone screening procedure and were randomized (Groups I and II only) or enrolled (Group III). | |
| Subject analysis set title | MMRV Per Protocol Population (PP - MMRV) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects who actually received one study vaccination correctly, provided evaluable serum samples at the relevant time points, were seronegative at baseline for any of the four antigens (MMRV analyses only), were included in the analysis of those antigens, and had no major protocol deviation as defined prior to unblinding. These subjects would have received either ProQuad™ or M-M-R™II + Varivax™. | |
| Subject analysis set title | MenACWY Per Protocol Population (PP - MenACWY) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All subjects who actually received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, were included in the analysis of that antigen, and had no major protocol deviation as defined prior to unblinding. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects in the Exposed Population who provided post-baseline safety data. | |

Primary: 1. Percentages of Subjects With a Seroresponse to Measles, Mumps, Rubella and Varicella Following Concomitant Administration of MMRV Vaccine With MenACWY Vaccine

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|--|--|
| End point title | 1. Percentages of Subjects With a Seroresponse to Measles, Mumps, Rubella and Varicella Following Concomitant Administration of MMRV Vaccine With MenACWY Vaccine ^[1] |
| End point description: Percentages of subjects with seroresponses to measles, mumps, rubella and varicella after one dose of MMRV vaccine (at 12 months) when given concomitantly with MenACWY vaccine compared to when MMRV vaccine was given alone, are reported. Seroresponse was defined as the percentage of initially seronegative subjects who show seroconversion to measles (≥ 255 mIU/mL), mumps (≥ 10 ELISA Ab units), rubella (≥ 10 IU/mL) and varicella (≥ 5 gp ELISA units/mL). Immunogenicity to measles, mumps, rubella and varicella at 6 weeks after vaccination with one dose of MMRV given concomitantly with MenACWY was considered non-inferior to immunogenicity of MMRV administered alone if the lower limit of two-sided 95% CI of the difference in | |

the percentage of subjects with seroconversion for measles, mumps, and rubella was greater than -5%, and seroprotection for varicella was greater than -10%.

The analysis was performed on the MMRV Per Protocol Population.

| | |
|--------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| 6 weeks post vaccination | |

Notes:

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

| End point values | ACWY + MMRV | MMRV | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 370 | 515 | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Measles (N=350,467) | 98 (96 to 99) | 99 (98 to 100) | | |
| Mumps (N=365,499) | 98 (96 to 99) | 96 (94 to 98) | | |
| Rubella (370,515) | 95 (93 to 97) | 97 (95 to 98) | | |
| Varicella (N=337,459) | 96 (94 to 98) | 98 (96 to 99) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Non-inferiority of immune response to measles |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority of immune response to measles following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for measles was greater than -5%, at 6 weeks after MMRV vaccination.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v MMRV |
| Number of subjects included in analysis | 885 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 0.5 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Non-inferiority of immune response to mumps |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority of immune response to mumps following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for mumps was greater than -5%, at 6

weeks after MMRV vaccination.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v MMRV |
| Number of subjects included in analysis | 885 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 3.7 |

Statistical analysis title

Non-inferiority of immune response to rubella

Statistical analysis description:

Non-inferiority of immune response to rubella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for rubella was greater than -5%, at 6 weeks after MMRV vaccination.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v MMRV |
| Number of subjects included in analysis | 885 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.5 |
| upper limit | 0.8 |

Statistical analysis title

Non-inferiority of immune response to varicella

Statistical analysis description:

Non-inferiority of immune response to varicella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of MenACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for varicella was greater than -10%, at 6 weeks after MMRV vaccination.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v MMRV |
| Number of subjects included in analysis | 885 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | -1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 1.2 |

Primary: 2. Percentages of Subjects With Serum Bactericidal Titers $\geq 1:8$ Following Concomitant Administration of MenACWY Vaccine With MMRV Vaccine.

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|-----------------|--|
| End point title | 2. Percentages of Subjects With Serum Bactericidal Titers $\geq 1:8$ Following Concomitant Administration of MenACWY Vaccine With MMRV Vaccine. ^[2] |
|-----------------|--|

End point description:

Percentages of subjects with hSBA $\geq 1:8$, against N.meningitidis serogroups A, C, W-135, and Y following two doses of MenACWY vaccine (at 7-9 months and 12 months) when concomitantly administered with MMRV vaccine (12 months) compared to when MenACWY vaccine was given alone, are reported. The serum bactericidal antibodies directed against N.meningitidis serogroups A, C, W-135, and Y, were measured by human complement Serum Bactericidal Assay (hSBA). The immune response of MenACWY given concomitantly with MMRV was considered non-inferior to the immunogenicity of MenACWY administered alone if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ at 6 weeks after the second dose of MenACWY given to 12-month old toddlers {P MMRV+MenACWY minus P MenACWY} was greater than -10% for each serogroup. The analysis was performed on the MenACWY Per Protocol population.

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

End point timeframe:

6 weeks post vaccination

Notes:

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

| End point values | ACWY + MMRV | ACWY | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 384 | 379 | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Serogroup A | 88 (84 to 91) | 88 (84 to 91) | | |
| Serogroup C (N=204,195) | 100 (98 to 100) | 100 (98 to 100) | | |
| Serogroup W-135 (N=204,196) | 100 (97 to 100) | 98 (96 to 100) | | |
| Serogroup Y (N=200,198) | 98 (95 to 99) | 96 (93 to 99) | | |

Statistical analyses

| | |
|----------------------------|-------------------------------------|
| Statistical analysis title | non-inferiority against serogroup A |
|----------------------------|-------------------------------------|

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup A when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone. The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater

than -10% for each serogroup.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v ACWY |
| Number of subjects included in analysis | 763 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | 4.5 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | non-inferiority against serogroup C |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup C when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.

The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v ACWY |
| Number of subjects included in analysis | 763 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 1.9 |

| | |
|-----------------------------------|---|
| Statistical analysis title | non-inferiority against serogroup W-135 |
|-----------------------------------|---|

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup W-135 when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.

The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

| | |
|-------------------|--------------------|
| Comparison groups | ACWY + MMRV v ACWY |
|-------------------|--------------------|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 763 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.3 |
| upper limit | 3.9 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | non-inferiority against serogroup Y |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Non-inferiority of immune response to MenACWY against serogroup Y when administered concomitantly with MMRV vaccine as compared to MenACWY vaccine given alone.

The immune response of MenACWY + MMRV group was considered non-inferior to that of MenACWY group if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA $\geq 1:8$ at 6 weeks after the second dose of MenACWY given to 12 month old toddlers was greater than -10% for each serogroup.

| | |
|---|-----------------------------|
| Comparison groups | ACWY + MMRV v ACWY |
| Number of subjects included in analysis | 763 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 5.3 |

Primary: 3. Percentages of Subjects With hSBA $\geq 1:8$ Following Two Doses of MenACWY Vaccine

| | |
|-----------------|--|
| End point title | 3. Percentages of Subjects With hSBA $\geq 1:8$ Following Two Doses of MenACWY Vaccine ^{[3][4]} |
|-----------------|--|

End point description:

The antibody response following two doses of MenACWY vaccine (at 7-9 months and 12 months) was considered adequate if the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA $\geq 1:8$, at 6 weeks following the second dose of MenACWY, was greater than 85% for serogroups C, W-135, or Y and greater than 65% for serogroup A. The analysis was performed on the MenACWY Per Protocol population.

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

End point timeframe:

6 weeks post second vaccination dose

Notes:

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

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

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

| End point values | ACWY | | | |
|----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 379 | | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Serogroup A | 88 (84 to 91) | | | |
| Serogroup C (N=195) | 100 (98 to 100) | | | |
| Serogroup W-135 (N=196) | 98 (96 to 100) | | | |
| Serogroup Y (N=198) | 96 (93 to 99) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Percentages of Subjects With hSBA $\geq 1:4$ Following Two Doses of MenACWY Vaccine

| | |
|-----------------|---|
| End point title | 4. Percentages of Subjects With hSBA $\geq 1:4$ Following Two Doses of MenACWY Vaccine ^[5] |
|-----------------|---|

End point description:

The percentages of subjects with hSBA $\geq 1:4$ directed against N. meningitidis serogroups A, C, W-135, and Y following two doses of MenACWY vaccine (at 7- 9 and 12 months of age) when given concomitantly with MMRV vaccine (at 12 months) compared to when MenACWY vaccine was given alone, are reported.

The analysis was performed on the MenACWY Per Protocol population.

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

End point timeframe:

6 weeks post second vaccination dose

Notes:

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

| End point values | ACWY + MMRV | ACWY | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 384 | 379 | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Serogroup A | 90 (86 to 92) | 91 (87 to 93) | | |
| Serogroup C (N=204,195) | 100 (98 to 100) | 100 (98 to 100) | | |
| Serogroup W-135 (N=204,196) | 100 (97 to 100) | 99 (96 to 100) | | |
| Serogroup Y (N=200,198) | 98 (95 to 99) | 98 (95 to 99) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Geometric Mean Titers Against Serogroups A, C, W-135 and Y, Following Two Doses of MenACWY Vaccine

| | |
|-----------------|--|
| End point title | 5. Geometric Mean Titers Against Serogroups A, C, W-135 and Y, Following Two Doses of MenACWY Vaccine ^[6] |
|-----------------|--|

End point description:

The geometric mean titers (GMTs) directed against *N. meningitidis* serogroups A, C, W-135 and Y, following two doses of MenACWY vaccine (at 7-9 months and 12 months of age), when given concomitantly with MMRV vaccine (at 12 months) compared to when MenACWY vaccine was given alone, are reported.

The analysis was performed on the MenACWY Per Protocol population.

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

End point timeframe:

6 weeks post second vaccination dose

Notes:

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

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

| End point values | ACWY + MMRV | ACWY | | |
|--|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 384 | 379 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Serogroup A | 39 (34 to 45) | 37 (32 to 42) | | |
| Serogroup C (N=204,195) | 194 (170 to 220) | 180 (158 to 205) | | |
| Serogroup W-135 (N=204,196) | 132 (113 to 155) | 119 (101 to 139) | | |
| Serogroup Y (N=200,198) | 97 (81 to 116) | 88 (73 to 105) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Geometric Mean Titers Against Measles, Mumps, Rubella and Varicella Following One Dose of MMRV Vaccine

| | |
|-----------------|--|
| End point title | 6. Geometric Mean Titers Against Measles, Mumps, Rubella and Varicella Following One Dose of MMRV Vaccine ^[7] |
|-----------------|--|

End point description:

The GMTs directed against measles, mumps, rubella and varicella, following one dose of MMRV vaccine (at 12 months) when given concomitantly with MenACWY vaccine compared to when MMRV vaccine was given alone, are reported.

The analysis was performed on the MMRV Per Protocol population.

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

End point timeframe:

6 weeks post vaccination

Notes:

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

| End point values | ACWY + MMRV | MMRV | | |
|--|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 377 | 518 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Pre-dose, Measles (N=357,470) | 74 (71 to 77) | 74 (71 to 77) | | |
| Post-dose, Measles (N=350,467) | 4049 (3701 to 4430) | 3632 (3350 to 3938) | | |
| Pre-dose, Mumps (N=372,502) | 5 (5 to 5) | 5 (5 to 5) | | |
| Post-dose, Mumps (N=365,499) | 97 (89 to 107) | 81 (75 to 88) | | |
| Pre-dose, Rubella | 5 (5 to 5) | 5 (5 to 5) | | |
| Post-dose, Rubella (370,515) | 57 (52 to 62) | 56 (52 to 61) | | |
| Pre-dose, Varicella (N=344,461) | 0.63 (0.63 to 0.63) | 0.63 (0.63 to 0.63) | | |
| Post-dose, Varicella (N=337,459) | 19 (17 to 20) | 18 (17 to 19) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Percentages of Subjects Showing Seroconversion Response to Varicella Following Concomitant Administration of MMRV With MenACWY Vaccine

| | |
|-----------------|--|
| End point title | 7. Percentages of Subjects Showing Seroconversion Response to Varicella Following Concomitant Administration of MMRV With MenACWY Vaccine ^[8] |
|-----------------|--|

End point description:

The percentages of subjects showing seroconversion response to varicella after concomitant administration of MMRV vaccine (at 12 months) with MenACWY vaccine compared to when MMRV vaccine is given alone, is reported.

Seroconversion for varicella is defined as the percentage of subjects who show pre-vaccination antibody titer <1.25 gp ELISA units/mL to a post-vaccination antibody titer ≥1.25 gp ELISA units/mL.

The analysis was performed on the MMRV Per Protocol population.

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

End point timeframe:

6 weeks post vaccination

Notes:

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

| End point values | ACWY + MMRV | MMRV | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 337 | 459 | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Varicella | 99 (97 to 100) | 99 (98 to 100) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Non-inferiority of immune response to varicella |
| Statistical analysis description: | |
| Non-inferiority of immune response to varicella following one dose of MMRV administered concomitantly with MenACWY as compared to MMRV given alone. The immune response of ACWY+MMRV group was considered non-inferior to that of MMRV group if the lower limit of the two-sided 95% CI of the difference in the percentage of subjects with seroconversion for varicella was greater than -10%, at 6 weeks after MMRV vaccination. | |
| Comparison groups | ACWY + MMRV v MMRV |
| Number of subjects included in analysis | 796 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | 95% Confidence Intervals |
| Parameter estimate | Percentage group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4 |
| upper limit | 0.8 |

Secondary: 8. Percentages of Subjects With hSBA $\geq 1:4$ and hSBA $\geq 1:8$ Following One Dose of MenACWY Vaccine

| | |
|---|--|
| End point title | 8. Percentages of Subjects With hSBA $\geq 1:4$ and hSBA $\geq 1:8$ Following One Dose of MenACWY Vaccine ^[9] |
| End point description: | |
| The percentages of subjects with hSBA $\geq 1:4$ and hSBA $\geq 1:8$ after one dose of MenACWY vaccine (at 7-9 months), are reported. | |
| The analysis was performed on the MenACWY Per Protocol population. | |
| End point type | Secondary |
| End point timeframe: | |
| 1 month post first vaccination dose | |
| Notes: | |
| [9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. | |
| Justification: There was no statistical null hypothesis associated with this immunogenicity objective. | |

| End point values | ACWY | | | |
|----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 349 | | | |
| Units: Percentages of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| Serogroup A hSBA $\geq 1:4$ | 63 (57 to 68) | | | |
| Serogroup A hSBA $\geq 1:8$ | 50 (45 to 56) | | | |

| | | | | |
|---|---------------|--|--|--|
| Serogroup C (N=199) hSBA \geq 1:4 | 93 (88 to 96) | | | |
| Serogroup C (N=199) hSBA \geq 1:8 | 88 (83 to 92) | | | |
| Serogroup W-135 (N=199) hSBA \geq 1:4 | 48 (41 to 55) | | | |
| Serogroup W-135 (N=199) hSBA \geq 1:8 | 37 (30 to 44) | | | |
| Serogroup Y (N=196) hSBA \geq 1:4 | 41 (34 to 49) | | | |
| Serogroup Y (N=196) hSBA \geq 1:8 | 31 (24 to 38) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 9. Geometric Mean Titers After One Dose of MenACWY Vaccine

| | |
|-----------------|--|
| End point title | 9. Geometric Mean Titers After One Dose of MenACWY |
|-----------------|--|

End point description:

The immunogenicity of one dose of MenACWY vaccine given at 7 to 9 months of age was assessed in terms of GMTs directed against N.meningitidis serogroups A, C, W-135, and Y.
The analysis was performed on the MenACWY Per Protocol population.

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

End point timeframe:

1 month post first vaccination dose

Notes:

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

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

| End point values | ACWY | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 349 | | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Serogroup A | 8.16 (6.96 to 9.58) | | | |
| Serogroup C (N=199) | 26 (22 to 31) | | | |
| Serogroup W-135 (N=199) | 5.11 (4.15 to 6.29) | | | |
| Serogroup Y (N=196) | 4.09 (3.36 to 4.98) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Number of Subjects Reporting Solicited Local and Systemic Adverse Events After Any Vaccination

| | |
|-----------------|--|
| End point title | 10. Number of Subjects Reporting Solicited Local and Systemic Adverse Events After Any Vaccination |
|-----------------|--|

End point description:

Safety and tolerability of MenACWY and MMRV vaccines when given concomitantly compared to when either MenACWY or MMRV vaccine was administered alone is reported in terms of the number of subjects with local and systemic adverse events after any vaccination.

Systemic reactions including axillary temperature with onset during the first 7 days after any study vaccination were reported. These included the following systemic reactions: Measles-like rash, Rubella-like rash, Varicella-like rash, injection site rash, Mumps-like symptoms and axillary temperature. The analysis was done on the safety population.

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

End point timeframe:

Up to 7 days after each study vaccine injection.

| End point values | ACWY + MMRV | ACWY | MMRV | |
|---|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 500 | 500 | 597 | |
| Units: Subjects | | | | |
| Any Local | 278 | 298 | 316 | |
| Injection (Inj.) site Tenderness [MenACWY] | 133 | 129 | 0 | |
| Inj. site Erythema [MenACWY] | 153 | 159 | 0 | |
| Inj. site Induration [MenACWY] | 74 | 74 | 0 | |
| Inj. site Tenderness [MMRV (N=455,424,592)] | 105 | 102 | 179 | |
| Inj. site Erythema [MMRV (N=456,425,593)] | 156 | 145 | 224 | |
| Inj. site Induration [MMRV (456,424,593)] | 90 | 60 | 102 | |
| Any Systemic Reaction | 371 | 372 | 381 | |
| Rash (N=500,499,595) | 54 | 44 | 46 | |
| Change in eating habits (N=475,483,550) | 132 | 136 | 105 | |
| Sleepiness (N=500,499,595) | 219 | 199 | 197 | |
| Persistent crying (N=475,483,550) | 135 | 152 | 109 | |
| Irritability (N=500,500,595) | 273 | 298 | 298 | |
| Vomiting (N=500,499,595) | 66 | 74 | 36 | |
| Diarrhea (N=500,499,595) | 120 | 123 | 107 | |
| Fever (≥ 38C) (N=499,500,596) | 58 | 78 | 42 | |
| Analgesic Antipyr. Meds (N=499,499,594) | 208 | 254 | 203 | |

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Number of Subjects Reporting Unsolicited Adverse Events After Vaccination

| | |
|-----------------|---|
| End point title | 11. Number of Subjects Reporting Unsolicited Adverse Events After Vaccination |
|-----------------|---|

End point description:

The safety profile of MenACWY and MMRV vaccines when given concomitantly as compared to when

MenACWY or MMRV was given alone is reported in terms of number of subjects reporting unsolicited adverse events (AEs), medically significant adverse events and serious adverse events (SAEs) after vaccination.

The analysis was done on the safety population.

| | |
|---------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1- Day 180 (Throughout the study) | |

| End point values | ACWY + MMRV | ACWY | MMRV | |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 500 | 500 | 597 | |
| Units: Subjects | | | | |
| Any AEs | 335 | 353 | 311 | |
| At least possibly related AEs | 70 | 63 | 2 | |
| Serious AEs | 18 | 19 | 9 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All solicited adverse events (AEs) were collected up to Day 7 after each vaccination.

All SAEs and unsolicited AEs were collected throughout the study (Day 1-Day 180).

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | ACWY + MMRV |
|-----------------------|-------------|

Reporting group description:

Subjects in this group received 2 injections of MenACWY at 7-9 and 12 months; second injection administered concomitantly with MMRV.

| | |
|-----------------------|------|
| Reporting group title | MMRV |
|-----------------------|------|

Reporting group description:

Subjects in this group received 1 injection of MMRV vaccine at 12 months of age.

| | |
|-----------------------|------|
| Reporting group title | ACWY |
|-----------------------|------|

Reporting group description:

Subjects in this group received 2 injections of the MenACWY vaccine at 7-9 and 12 months of age followed by 1 injection of MMRV at 13.5 months

| Serious adverse events | ACWY + MMRV | MMRV | ACWY |
|---|------------------|-----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 500 (3.60%) | 9 / 597 (1.51%) | 19 / 500 (3.80%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Gun shot wound | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Febrile convulsion | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 2 / 500 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tethered cord syndrome | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachypnoea | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 2 / 597 (0.34%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 500 (0.40%) | 0 / 597 (0.00%) | 3 / 500 (0.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impetigo | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumococcal sepsis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 2 / 597 (0.34%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 2 / 500 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic shock syndrome | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 1 / 597 (0.17%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 500 (0.60%) | 1 / 597 (0.17%) | 3 / 500 (0.60%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Feeding disorder | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 500 (0.00%) | 0 / 597 (0.00%) | 1 / 500 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 500 (0.20%) | 0 / 597 (0.00%) | 0 / 500 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | ACWY + MMRV | MMRV | ACWY |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 433 / 500 (86.60%) | 482 / 597 (80.74%) | 442 / 500 (88.40%) |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 219 / 500 (43.80%) | 197 / 597 (33.00%) | 199 / 500 (39.80%) |
| occurrences (all) | 424 | 290 | 443 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 219 / 500 (43.80%) | 224 / 597 (37.52%) | 230 / 500 (46.00%) |
| occurrences (all) | 484 | 263 | 466 |
| Injection site pain | | | |

| | | | |
|---|---------------------------|---------------------------|---------------------------|
| subjects affected / exposed occurrences (all) | 163 / 500 (32.60%) 345 | 180 / 597 (30.15%) 233 | 188 / 500 (37.60%) 318 |
| Injection site induration subjects affected / exposed occurrences (all) | 128 / 500 (25.60%) 254 | 102 / 597 (17.09%) 130 | 115 / 500 (23.00%) 221 |
| Pyrexia subjects affected / exposed occurrences (all) | 90 / 500 (18.00%) 116 | 70 / 597 (11.73%) 84 | 114 / 500 (22.80%) 160 |
| Crying subjects affected / exposed occurrences (all) | 135 / 500 (27.00%) 261 | 109 / 597 (18.26%) 161 | 152 / 500 (30.40%) 312 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 125 / 500 (25.00%) 220 | 114 / 597 (19.10%) 185 | 128 / 500 (25.60%) 255 |
| Teething subjects affected / exposed occurrences (all) | 41 / 500 (8.20%) 51 | 41 / 597 (6.87%) 48 | 60 / 500 (12.00%) 73 |
| Vomiting subjects affected / exposed occurrences (all) | 68 / 500 (13.60%) 113 | 43 / 597 (7.20%) 60 | 79 / 500 (15.80%) 123 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 26 / 500 (5.20%) 29 | 29 / 597 (4.86%) 29 | 30 / 500 (6.00%) 34 |
| Rash subjects affected / exposed occurrences (all) | 76 / 500 (15.20%) 128 | 87 / 597 (14.57%) 135 | 52 / 500 (10.40%) 102 |
| Psychiatric disorders | | | |
| Irritability subjects affected / exposed occurrences (all) | 273 / 500 (54.60%) 654 | 299 / 597 (50.08%) 481 | 299 / 500 (59.80%) 788 |
| Eating disorder subjects affected / exposed occurrences (all) | 132 / 500 (26.40%) 260 | 105 / 597 (17.59%) 166 | 136 / 500 (27.20%) 292 |
| Infections and infestations | | | |

| | | | |
|---|--------------------------|------------------------|---------------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 71 / 500 (14.20%) 86 | 20 / 597 (3.35%) 22 | 92 / 500 (18.40%) 110 |
| Otitis media subjects affected / exposed occurrences (all) | 92 / 500 (18.40%) 126 | 40 / 597 (6.70%) 42 | 120 / 500 (24.00%) 160 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 12 November 2007 | Substantial changes: to add requested new primary immunogenicity objective; to update the immunogenicity criteria to incorporate the new third co-primary objective; to add the null hypothesis for the two-dose immunogenicity; to add statistical power computations for the two-dose MenACWY objective; to clarify SAE reporting; to clarify major deviations and demographic data analysis; to update analysis of immunogenicity criteria for new co-primary objective. |
| 02 October 2008 | Clarifications on study procedures and terms. |
| 17 February 2009 | Due to a shortage of ProQuad on the US market, for subjects enrolled into the trial in Groups 1 and 2, M-M-R II and Varivax to be administered in place of ProQuad. |
| 28 May 2009 | Statistical and operational changes to allow for use of M-M-R® II and Varivax® instead of ProQuad. |
| 04 March 2010 | To allow for use of frozen ProQuad and change storage temperatures. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|-----------------------------|--------------|
| 16 January 2009 | Due to shortage of ProQuad. | 03 July 2009 |

Notes:

Limitations and caveats

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

N/A

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22504039>