



Clinical trial results:

A Phase 3B, Open Label, Multi-Center Study to Evaluate the Safety, Tolerability and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered Alone to Healthy Infants According to Different Immunization Schedules and to Healthy Children Aged 2 to 10 Years

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-021528-81 |
| Trial protocol | ES HU |
| Global end of trial date | 01 July 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 April 2016 |
| First version publication date | 15 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | V72_28 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01339923 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Vaccines and Diagnostics |
| Sponsor organisation address | Via Fiorentina 1, Siena, Italy, 53100 |
| Public contact | Study Start-up Associate, ICON Clinical Research Ltd, +36 28471689, zsuzsanna.tribel@iconplc.com |
| Scientific contact | Study Start-up Associate, ICON Clinical Research Ltd, +36 28471689, zsuzsanna.tribel@iconplc.com |
| Sponsor organisation name | Novartis Vaccines and Diagnostics |
| Sponsor organisation address | Via Fiorentina 1, Siena, Italy, 53100 |
| Public contact | Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com |
| Scientific contact | Posting Director, Novartis Vaccines and Diagnostics, RegistryContactVaccinesUS@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan | EMA-000139-PIP01-07 |

| | |
|--|-----|
| number(s) | |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| Notes: | |

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 July 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2015 |
| Was the trial ended prematurely? | No |
| Notes: | |

General information about the trial

Main objective of the trial:

To demonstrate a sufficient immune response following rMenB+OMV NZ vaccination, when given as a two dose primary series to healthy infants at 3 1/2 and 5 months of age or at 6 and 8 months of age, as measured by the percentage of subjects with serum bactericidal activity (SBA) titers of at least 4, at 1 month after the second rMenB+OMV NZ dose, directed against MenB indicator strains H44/76, 5/99 and NZ98/254.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 06 April 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 | Brazil: 417 |
| Country: Number of subjects enrolled | Peru: 59 |
| Country: Number of subjects enrolled | Spain: 653 |
| Country: Number of subjects enrolled | Hungary: 280 |
| Worldwide total number of subjects | 1409 |
| EEA total number of subjects | 933 |

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) | 1005 |
| Children (2-11 years) | 404 |
| 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:

The study was conducted in a total of a total of 26 sites; 4 sites in Brazil, 3 sites in Peru, 10 sites in Hungary, 9 sites in Spain.

Pre-assignment

Screening details:

All enrolled subjects were included in the study.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | B_2h3h5_11 |

Arm description:

Subjects approximately 2.5 months of age received 3 dose primary vaccination of rMenB+OMV NZ at 2.5, 3.5, 5 months of age, followed by a booster dose at 11 months of age.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

rMenB+OMV NZ Vaccine: Administration was done intramuscularly (IM), 3 doses + booster, of 0.5 mL each.

| | |
|------------------|----------|
| Arm title | B_3h5_11 |
|------------------|----------|

Arm description:

Subjects approximately 3.5 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

rMenB+OMV NZ Vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each.

| | |
|------------------|---------|
| Arm title | B_68_11 |
|------------------|---------|

Arm description:

Subjects approximately 6 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 6 and 8 months of age, followed by a booster dose at 11 months of age.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|--|
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: rMenB+OMV NZ Vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each. | |
| Arm title | B_02_2_5 |
| Arm description: Subjects 2-5 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: rMenB+OMV NZ vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each. | |
| Arm title | BC_35_12 |
| Arm description: Subjects 3 months of age received rMenB+OMV NZ + MenC-CRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone dose at 7 months of age. | |
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine Meningococcal (group C) oligosaccharide diphtheria CRM-197 conjugate vaccine Synflorix |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ MenC-CRM Synflorix |
| Pharmaceutical forms | Powder and solvent for suspension for injection, Suspension for injection, Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |
| Dosage and administration details: rMenB+OMV NZ vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each. MenC-CRM vaccine: Administration was done IM, 2 doses booster, of 0.5 mL each. Synflorix: Administration was done IM, 3 doses + booster. | |
| Arm title | C_35_12 |
| Arm description: Subjects 3 months of age received MenCCRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone at 7 months of age and rMenB+OMV NZ alone at 13 and 15 months of age. | |
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine Meningococcal (group C) oligosaccharide diphtheria CRM-197 conjugate vaccine Synflorix |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ MenC-CRM Synflorix |
| Pharmaceutical forms | Powder and solvent for suspension for injection, Suspension for injection, Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |
| Dosage and administration details: rMenB+OMV NZ vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each. MenC-CRM vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each. Synflorix: Administration was done IM, 3 doses + booster. | |

| | |
|--|---|
| Arm title | B_02_6_10 |
| Arm description: Subjects 6-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Arm type | Experimental |
| Investigational medicinal product name | Meningococcal (group B) multicomponent recombinant adsorbed vaccine |
| Investigational medicinal product code | |
| Other name | rMenB+OMV NZ |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

rMenB+OMV NZ vaccine: Administration was done IM, 2 doses + booster, of 0.5 mL each.

| Number of subjects in period 1 | B_2h3h5_11 | B_3h5_11 | B_68_11 |
|---------------------------------------|------------|----------|---------|
| Started | 253 | 250 | 251 |
| Completed | 239 | 234 | 243 |
| Not completed | 14 | 16 | 8 |
| Consent withdrawn by subject | 7 | 11 | 6 |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Inappropriate enrollment | 1 | - | - |
| Unable to classify | 1 | - | 1 |
| Lost to follow-up | 4 | 4 | - |
| Protocol deviation | - | - | - |

| Number of subjects in period 1 | B_02_2_5 | BC_35_12 | C_35_12 |
|---------------------------------------|----------|----------|---------|
| Started | 104 | 126 | 125 |
| Completed | 100 | 117 | 111 |
| Not completed | 4 | 9 | 14 |
| Consent withdrawn by subject | 1 | 3 | 2 |
| Adverse event, non-fatal | - | - | 1 |
| Inappropriate enrollment | - | 1 | - |
| Unable to classify | - | 1 | 5 |
| Lost to follow-up | 3 | 1 | 5 |
| Protocol deviation | - | 3 | 1 |

| Number of subjects in period 1 | B_02_6_10 |
|---------------------------------------|-----------|
| Started | 300 |
| Completed | 295 |
| Not completed | 5 |
| Consent withdrawn by subject | 4 |
| Adverse event, non-fatal | - |

| | |
|--------------------------|---|
| Inappropriate enrollment | - |
| Unable to classify | - |
| Lost to follow-up | 1 |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|--|------------|
| Reporting group title | B_2h3h5_11 |
| Reporting group description: Subjects approximately 2.5 months of age received 3 dose primary vaccination of rMenB+OMV NZ at 2.5, 3.5, 5 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_3h5_11 |
| Reporting group description: Subjects approximately 3.5 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_68_11 |
| Reporting group description: Subjects approximately 6 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 6 and 8 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_02_2_5 |
| Reporting group description: Subjects 2-5 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Reporting group title | BC_35_12 |
| Reporting group description: Subjects 3 months of age received rMenB+OMV NZ + MenC-CRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone dose at 7 months of age. | |
| Reporting group title | C_35_12 |
| Reporting group description: Subjects 3 months of age received MenCCRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone at 7 months of age and rMenB+OMV NZ alone at 13 and 15 months of age. | |
| Reporting group title | B_02_6_10 |
| Reporting group description: Subjects 6-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |

| Reporting group values | B_2h3h5_11 | B_3h5_11 | B_68_11 |
|---|------------|----------|---------|
| Number of subjects | 253 | 250 | 251 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: months | | | |
| arithmetic mean | 2 | 3 | 6 |
| standard deviation | ± 0.1 | ± 0.1 | ± 0 |

| | | | |
|---------------------------------------|-----|-----|-----|
| Gender categorical Units: Subjects | | | |
| Female | 117 | 124 | 127 |
| Male | 136 | 126 | 124 |

| | | | |
|---|----------|----------|---------|
| Reporting group values | B_02_2_5 | BC_35_12 | C_35_12 |
| Number of subjects | 104 | 126 | 125 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: months | | | |
| arithmetic mean | 3.958 | 3 | 3 |
| standard deviation | ± 1.117 | ± 0.2 | ± 0.1 |
| Gender categorical Units: Subjects | | | |
| Female | 49 | 74 | 59 |
| Male | 55 | 52 | 66 |

| | | | |
|---|-----------|---|--|
| Reporting group values | B_02_6_10 | Total | |
| Number of subjects | 300 | 1409 | |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | 0 0 0 0 0 0 0 0 0 | |
| Age continuous Units: months | | | |
| arithmetic mean | 8.074 | - | |
| standard deviation | ± 1.404 | | |
| Gender categorical Units: Subjects | | | |
| Female | 149 | 699 | |
| Male | 151 | 710 | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | B_2h3h5_11 |
| Reporting group description: Subjects approximately 2.5 months of age received 3 dose primary vaccination of rMenB+OMV NZ at 2.5, 3.5, 5 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_3h5_11 |
| Reporting group description: Subjects approximately 3.5 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_68_11 |
| Reporting group description: Subjects approximately 6 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 6 and 8 months of age, followed by a booster dose at 11 months of age. | |
| Reporting group title | B_02_2_5 |
| Reporting group description: Subjects 2-5 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Reporting group title | BC_35_12 |
| Reporting group description: Subjects 3 months of age received rMenB+OMV NZ + MenC-CRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone dose at 7 months of age. | |
| Reporting group title | C_35_12 |
| Reporting group description: Subjects 3 months of age received MenCCRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone at 7 months of age and rMenB+OMV NZ alone at 13 and 15 months of age. | |
| Reporting group title | B_02_6_10 |
| Reporting group description: Subjects 6-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Subject analysis set title | All Enrolled Set |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All subjects enrolled in the study, ie., all screened subjects who provided informed consent and provided demographic and/or baseline assessments, regardless of the subjects' randomization and treatment status in the trial. | |
| Subject analysis set title | Full Analysis set (FAS; Immunogenicity; Primary series) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects in enrolled population who received at least one rMenB+OMV NZ dose or MenC-CRM (group C3512) and provided an evaluable serum sample at relevant time points (visit 4 for group B_2h3h5_11 and visit 3 for groups B_3h5_11, B_68_11, B_02, BC_35_12 and C_35_12). | |
| Subject analysis set title | Full Analysis set (FAS; Immunogenicity; Post first dose respon |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects enrolled in Groups B_2h3h5_11b, B_3h5_11b and B_68_11b who received at least one rMenB+OMV NZ dose and provided an evaluable serum sample at 1, 1.5 and 2 months, respectively, after the first vaccination (visit 2). | |
| Subject analysis set title | Full Analysis set (Immunogenicity; persistence) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All subjects in enrolled population who received at least one rMenB+OMV NZ dose or MenC-CRM (group | |

C_35_12) and provided an evaluable serum sample at relevant time points (visit 5 for groups B_2h_3h511, BC_35_12, C_35_12 and visit 4 for groups B_3h5_11, B_68_11).

| | |
|----------------------------|---|
| Subject analysis set title | Full Analysis set (Immunogenicity; Booster) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All subjects in enrolled population who received at least one rMenB+OMV NZ dose or MenC-CRM (group C_35_12) and provided an evaluable serum sample at relevant time points (visit 6 for groups B_2h_3h5_11, BC_35_12, C_35_12 and visit 5 for groups B_3h5_11, B_68_11).

| | |
|----------------------------|--|
| Subject analysis set title | Per protocol set (PPS; Immunogenicity; Primary series) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects in FAS population, who correctly received all doses of vaccine in primary series, provided evaluable serum sample at relevant time points (visit 4 for group B_2h3h5_11 and visit 3 for groups B_3h5_11, B_68_11, B_02, BC_35_12 and C_35_12) and have no major protocol deviations.

| | |
|----------------------------|--|
| Subject analysis set title | Per protocol set (PPS; Immunogenicity; Post first dose respons |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects in FAS population, who correctly received all doses of vaccine in primary series, provided evaluable serum sample at relevant time points (visit 5 for groups B_2h3h5_11, BC_35_12, C_35_12 and visit 4 for groups B_3h5_11, B_68_11) and have no major protocol deviations.

| | |
|----------------------------|--|
| Subject analysis set title | Per protocol set (Immunogenicity; Booster) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All subjects in FAS population, who correctly received all doses of vaccine in primary series and booster dose, provided evaluable serum sample at relevant time points (visit 6 for groups B_2h3h5_11, BC_35_12, C_35_12 and visit 5 for groups B_3h5_11, B_68_11) and have no major protocol deviations.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Overall safety set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects in the enrolled set, who received a study vaccination and provided solicited or unsolicited adverse event data.

| | |
|----------------------------|----------------------|
| Subject analysis set title | Solicited safety set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects in the enrolled set, who received a study vaccination and provided any solicited adverse event data or indicators of solicited adverse events

| | |
|----------------------------|------------------------|
| Subject analysis set title | Unsolicited safety set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects in the enrolled set, who received a study vaccination and provided unsolicited adverse event data.

| | |
|----------------------------|---------------|
| Subject analysis set title | B_2h3h5_11b |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects, approximately 2.5 months of age received 3 dose primary vaccination of rMenB+OMV NZ at 2.5, 3.5, 5 months of age, followed by a booster dose at 11 months of age. Blood draw at 3.5, 6, 11 and 12 months of age.

| | |
|----------------------------|---------------|
| Subject analysis set title | B_3h5_11b |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects, approximately 3.5 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age. Blood draw at 5, 11 and 12 months of age.

| | |
|----------------------------|----------|
| Subject analysis set title | B_68_11b |
|----------------------------|----------|

| | |
|---|-----------------|
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects, approximately 6 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age. Blood draw at 8, 9, 11 and 12 months of age. | |
| Subject analysis set title | B_02_2_5 |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects, 2-5 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Subject analysis set title | B_02_6_10 |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects, 6-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. | |
| Subject analysis set title | B_02 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects, 2-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start. rMenB + OMV NZ vaccine: 2 doses 2 months apart | |

Primary: Percentages of Subjects with Serum Bactericidal Activity Using Human Serum (hSBA) Titers ≥ 4 or hSBA Titers ≥ 5 (Strain M10713) Following a 2-dose Primary Series of rMenB+OMV Vaccination

| | |
|--|--|
| End point title | Percentages of Subjects with Serum Bactericidal Activity Using Human Serum (hSBA) Titers ≥ 4 or hSBA Titers ≥ 5 (Strain M10713) Following a 2-dose Primary Series of rMenB+OMV Vaccination ^{[1][2]} |
| End point description: Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254 and hSBA titers ≥ 5 against strain M10713 following 2-dose primary series of vaccination with rMenB+OMV NZ at 3.5 and 5 months of age or at 6 and 8 months of age. Analysis was done on Full analysis set (FAS)-Primary series. | |
| End point type | Primary |
| End point timeframe: 1 month after second vaccination | |

Notes:

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

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

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

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

| End point values | B_3h5_11 | B_68_11 | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 230 | 238 | | |
| Units: Percentages of subjects | | | | |
| number (confidence interval 97.5%) | | | | |
| H44/76 (hSBA ≥ 4 ; N=228, 234) | 100 (97 to 100) | 100 (97 to 100) | | |
| 5/99 (hSBA ≥ 4) | 100 (97 to 100) | 100 (98 to 100) | | |
| NZ98/254 (hSBA ≥ 4 ; N=230, 233) | 98 (95 to 99) | 99 (97 to 100) | | |
| M10713 (hSBA ≥ 5 ; N=181, 192) | 44 (35 to 52) | 73 (65 to 80) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 4 , hSBA Titers ≥ 5 (Strain M10713) and hSBA ≥ 8 Following a 3-dose Primary Series of rMenB+OMV Vaccination

| | |
|-----------------|--|
| End point title | Percentages of Subjects with hSBA Titers ≥ 4 , hSBA Titers ≥ 5 (Strain M10713) and hSBA ≥ 8 Following a 3-dose Primary Series of rMenB+OMV Vaccination ^[3] |
|-----------------|--|

End point description:

Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254; hSBA titers ≥ 5 against strain M10713 and hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713, following 3-dose primary series of vaccination with rMenB+OMV NZ at 2.5, 3.5 and 5 months of age. Analysis was done on FAS-primary series.

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

End point timeframe:

1 month after third vaccination

Notes:

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

| End point values | B_2h3h5_11 | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 238 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4 ; 1 month after 3rd vacc; N=237) | 100 (98 to 100) | | | |
| 5/99 (hSBA ≥ 4 ; 1 month after 3rd vacc) | 100 (98 to 100) | | | |
| NZ98/254 (hSBA ≥ 4 ; 1 month after 3rd vacc) | 99 (96 to 100) | | | |
| M10713 (hSBA ≥ 5 ; 1 month after 3rd vacc; N=197) | 55 (48 to 62) | | | |
| H44/76 (hSBA ≥ 8 ; 1 month after 3rd vacc; N=237) | 98 (96 to 100) | | | |
| 5/99 (hSBA ≥ 8 ; 1 month after 3rd vacc) | 100 (98 to 100) | | | |
| NZ98/254 (hSBA ≥ 8 ; 1 month after 3rd vacc) | 89 (85 to 93) | | | |
| M10713 (hSBA ≥ 8 ; 1 month after 3rd vacc; N=197) | 47 (40 to 54) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (Strain M10713) and hSBA ≥ 8 Following a 2-dose Catch-up Series of rMenB+OMV Vaccination

| | |
|-----------------|---|
| End point title | Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (Strain M10713) and hSBA ≥ 8 Following a 2-dose Catch-up Series of rMenB+OMV Vaccination |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254; hSBA titers ≥ 5 against strain M10713 and hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713; following 2-dose catch-up series of vaccination with rMenB+OMV NZ in healthy children aged 2-10 years (0, 2 month schedule). Analysis was done on FAS-primary series.

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

End point timeframe:

1 month after second vaccination

| End point values | B_02 | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 390 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4 ; 1 month after 2nd vacc; N=386) | 99 (97 to 100) | | | |
| 5/99 (hSBA ≥ 4 ; 1 month after 2nd vacc) | 99 (98 to 100) | | | |
| NZ98/254 (hSBA ≥ 4 ; 1 month after 2nd vacc; N=389) | 99 (97 to 100) | | | |
| M10713 (hSBA ≥ 5 ; 1 month after 2nd vacc; N=370) | 94 (91 to 96) | | | |
| H44/76 (hSBA ≥ 8 ; 1 month after 2nd vacc; N=386) | 98 (96 to 99) | | | |
| 5/99 (hSBA ≥ 8 ; 1 month after 2nd vacc) | 99 (98 to 100) | | | |
| NZ98/254 (hSBA ≥ 8 ; 1 month after 2nd vacc; N=389) | 95 (92 to 97) | | | |
| M10713 (hSBA ≥ 8 ; 1 month after 2nd vacc; N=370) | 92 (89 to 94) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects Achieving Four-fold Rise Over Baseline hSBA Titers Following a 2-dose Catch-up Series of rMenB+OMV Vaccination

| | |
|-----------------|--|
| End point title | Percentages of Subjects Achieving Four-fold Rise Over Baseline hSBA Titers Following a 2-dose Catch-up Series of rMenB+OMV Vaccination |
|-----------------|--|

End point description:

Immunogenicity was assessed in terms of percentages of subjects achieving 4-fold increase in hSBA

titers as compared to baseline against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254, M10713; following 2-dose catch-up series of vaccination with rMenB+OMV NZ in healthy children aged 2-10 years (0, 2 month schedule). Analysis was done on FAS- primary series.

| | |
|----------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 1 month after second vaccination | |

| End point values | B_02 | | | |
|---|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 388 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (1 month after 2nd vacc; N=385) | 96 (93 to 97) | | | |
| 5/99 (1 month after 2nd vacc) | 99 (97 to 100) | | | |
| NZ98/254 (1 month after 2nd vacc; N=387) | 93 (89 to 95) | | | |
| M10713 (1 month after 2nd vacc; N=352) | 46 (41 to 51) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean hSBA Titers (GMTs) Following 2 or 3 Dose Primary Series of Vaccination with rMenB+OMV

| | |
|-----------------|---|
| End point title | Geometric Mean hSBA Titers (GMTs) Following 2 or 3 Dose Primary Series of Vaccination with rMenB+OMV ^[4] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of Geometric mean hSBA titers (GMTs) against N meningitidis serogroup B indicator strains following 2 or 3 dose primary series of vaccination rMenB+OMV NZ (1 month after 3rd infant vaccination in B_2h3h5_11 and 1 month after 2nd infant vaccination in B_3h5_11, B_68_11 and B_02). Analysis was done on FAS-primary series.

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

End point timeframe:

1 month after primary series vaccination

Notes:

[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 | B_2h3h5_11 | B_3h5_11 | B_68_11 | B_02 |
|---|-----------------|------------------|------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 238 | 230 | 238 | 390 |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 (1 m after primary vacc; N=237,228,234,386) | 109 (92 to 130) | 132 (110 to 158) | 240 (201 to 287) | 121 (109 to 135) |

| | | | | |
|---|---------------------|---------------------|--------------------|------------------|
| 5/99 (1 m after primary vacc) | 795 (665 to 950) | 605 (502 to 729) | 1157 (964 to 1390) | 489 (442 to 541) |
| NZ98/254 1 m after primary vacc; N=238,230,233,389 | 34 (28 to 42) | 39 (31 to 48) | 65 (52 to 80) | 42 (38 to 47) |
| M10713 (1 m after primary vacc; N=197,181,192,370) | 4.86 (3.62 to 6.54) | 3.39 (2.48 to 4.64) | 9.96 (7.33 to 14) | 35 (31 to 39) |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean hSBA Titers (GMTs) After First Infant Vaccination with rMenB+OMV

| | |
|-----------------|---|
| End point title | Geometric Mean hSBA Titers (GMTs) After First Infant Vaccination with rMenB+OMV |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of Geometric mean hSBA titers (GMTs) against N meningitidis serogroup B indicator strains after the first infant vaccination in groups B_2h3h5_11b, B_3h5_11b and B_68_11b (after 1 month for group B_2h3h5_11b, 1.5 months for group B_2h3h5_11b and 2 months for group B_68_11b). Analysis was done on FAS-post first dose.

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

End point timeframe:

1, 1.5 or 2 months after first infant vaccination

| End point values | B_2h3h5_11b | B_3h5_11b | B_68_11b | |
|---|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 119 | 115 | 118 | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 1 month after 1st vacc; N=117,115,117 | 4.19 (3.29 to 5.35) | 5.7 (4.41 to 7.37) | 9.83 (7.59 to 13) | |
| 5/99 1 month after 1st vacc | 20 (15 to 27) | 30 (22 to 42) | 37 (27 to 52) | |
| NZ98/254 1 month after 1st vacc; N=118,114,117 | 2.87 (2.32 to 3.54) | 2.48 (1.98 to 3.11) | 2.84 (2.28 to 3.55) | |
| M10713 1 month after 1st vacc; N=95,99,95 | 2.59 (1.86 to 3.6) | 1.69 (1.21 to 2.36) | 1.62 (1.15 to 2.28) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 and hSBA ≥ 8 After First Infant Vaccination with rMenB+OMV

| | |
|-----------------|---|
| End point title | Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 and hSBA ≥ 8 After First Infant Vaccination with rMenB+OMV |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N

meningitidis serogroup B strains H44/76, 5/99, NZ98/254, hSBA titers ≥ 5 against strain M10713 and hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713 after the first infant vaccination in groups B_2h3h5_11b, B_3h5_11b and B_68_11b (at 3.5, 5, and 8 months of age respectively). Analysis was done on FAS-post first dose.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Post- first dose (1 month for B_2h3h5_11b, 1.5 month for B_3h5_11b and 2 months for B_68_11b after 1st vaccination) | |

| End point values | B_2h3h5_11b | B_3h5_11b | B_68_11b | |
|---|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 119 | 115 | 118 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4 ; Post 1st vacc; N=117,115,117) | 62 (52 to 70) | 72 (63 to 80) | 82 (74 to 89) | |
| 5/99 (hSBA ≥ 4 ; Post 1st vacc) | 91 (84 to 95) | 95 (89 to 98) | 92 (86 to 96) | |
| NZ98/254 (hSBA ≥ 4 ; Post 1st vacc; N=118,114,117) | 43 (34 to 53) | 39 (30 to 48) | 41 (32 to 50) | |
| M10713 (hSBA ≥ 5 ; Post1st vacc; N=95,99,95) | 31 (21 to 41) | 18 (11 to 27) | 17 (10 to 26) | |
| H44/76 (hSBA ≥ 8 ; Post 1st vacc; N=117,115,117) | 25 (17 to 34) | 38 (29 to 48) | 58 (49 to 67) | |
| 5/99 (hSBA ≥ 8 ; Post1st vacc) | 82 (73 to 88) | 90 (82 to 94) | 86 (79 to 92) | |
| NZ98/254 (hSBA ≥ 8 ; 1st vacc; N=118,114,117) | 13 (7 to 20) | 7 (3 to 13) | 13 (7 to 20) | |
| M10713 (hSBA ≥ 8 ; Post1st vacc; N=95,99,95) | 21 (13 to 31) | 15 (9 to 24) | 13 (7 to 21) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 and hSBA ≥ 8 Following a Booster Dose of rMenB +OMV Vaccination

| | |
|-----------------|---|
| End point title | Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 and hSBA ≥ 8 Following a Booster Dose of rMenB +OMV Vaccination ^[5] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254; hSBA titers ≥ 5 against strain M10713; hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713; following a booster dose of rMenB+OMV NZ given at 11 months of age (4th dose for B_2h3h5_11 and 3rd dose for B_3h5_11 and B_68_11). Analysis was done on FAS-booster.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 1 month post-booster 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 | B_2h3h5_11 | B_3h5_11 | B_68_11 | |
|--|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 233 | 228 | 239 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4, after booster; N=233,227,238) | 100 (98 to 100) | 100 (98 to 100) | 100 (98 to 100) | |
| 5/99 (hSBA ≥ 4, after booster) | 100 (98 to 100) | 100 (98 to 100) | 100 (98 to 100) | |
| NZ98/254 (hSBA ≥ 4, after booster; N=231,226,236) | 100 (98 to 100) | 99 (96 to 100) | 100 (98 to 100) | |
| M10713 (hSBA ≥ 5, after booster; N=203,181,193) | 83 (77 to 88) | 87 (81 to 91) | 83 (77 to 88) | |
| H44/76 (hSBA ≥ 8, after booster; N=233,227,238) | 100 (98 to 100) | 100 (98 to 100) | 100 (98 to 100) | |
| 5/99 (hSBA ≥ 8, after booster) | 100 (98 to 100) | 100 (98 to 100) | 100 (98 to 100) | |
| NZ98/254 (hSBA ≥ 8, after booster; N=231,226,236) | 95 (91 to 97) | 95 (91 to 98) | 97 (95 to 99) | |
| M10713 (hSBA ≥ 8, after booster; N=203,181,193) | 78 (72 to 84) | 83 (77 to 89) | 74 (67 to 80) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody Persistence in Terms of Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (M10713) and hSBA ≥ 8 Following 2 or 3-dose Primary Series of Vaccination with rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Antibody Persistence in Terms of Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (M10713) and hSBA ≥ 8 Following 2 or 3-dose Primary Series of Vaccination with rMenB+OMV NZ ^[6] |
|-----------------|---|

End point description:

Persistence of bactericidal antibodies at 11 months of age was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254; hSBA titers ≥ 5 against strain M10713; hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713 in subjects who previously received a primary series of 2 or 3-doses of rMenB+OMV NZ vaccine. Analysis was done on FAS-persistence.

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

End point timeframe:

11 months of age (persistence)

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 | B_2h3h5_11 | B_3h5_11 | B_68_11 | |
|---|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 235 | 233 | 238 | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4; 11 months of age; N=235,232,237) | 87 (82 to 91) | 86 (81 to 90) | 100 (98 to 100) | |

| | | | | |
|--|-----------------|---------------|-----------------|--|
| 5/99 (hSBA \geq 4; 11 months of age; N=234,230,235) | 100 (98 to 100) | 93 (89 to 96) | 100 (98 to 100) | |
| NZ98/254 hSBA \geq 4; 11 months of age; N=233,233,238) | 54 (47 to 60) | 41 (34 to 47) | 90 (85 to 93) | |
| M10713 (hSBA \geq 5; 11 months of age; N=199,177,188) | 33 (26 to 40) | 23 (17 to 30) | 42 (35 to 49) | |
| H44/76 (hSBA \geq 8; 11 months of age; N=235,232,237) | 64 (58 to 70) | 60 (53 to 66) | 96 (93 to 98) | |
| 5/99 (hSBA \geq 8; 11 months of age; N=234,230,235) | 94 (91 to 97) | 87 (82 to 91) | 99 (97 to 100) | |
| NZ98/254 hSBA \geq 8; 11 months of age; N=233,233,238) | 36 (30 to 43) | 12 (8 to 17) | 65 (58 to 71) | |
| M10713 (hSBA \geq 8; 11 months of age; N=199,177,188) | 24 (18 to 30) | 16 (11 to 22) | 36 (29 to 43) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody Persistence in Terms of Geometric Mean Titers Following 2 or 3-dose Primary Series of Vaccination with rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Antibody Persistence in Terms of Geometric Mean Titers Following 2 or 3-dose Primary Series of Vaccination with rMenB+OMV NZ ^[7] |
|-----------------|---|

End point description:

Persistence of bactericidal antibodies at 11 months of age was assessed in terms of GMTs against N meningitidis serogroup B indicator strains in subjects who previously received a primary series of 2 or 3-doses of rMenB+OMV NZ. Analysis was done on FAS-persistence.

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

End point timeframe:

11 months of age (persistence)

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 | B_2h3h5_11 | B_3h5_11 | B_68_11 | |
|--|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 235 | 233 | 238 | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 (Baseline; N=111,113,120) | 1.31 (1.09 to 1.57) | 1.34 (1.11 to 1.62) | 1.58 (1.32 to 1.9) | |
| H44/76 (11 moa; N=235,232,237) | 12 (9.64 to 14) | 12 (9.36 to 14) | 66 (54 to 81) | |
| 5/99 (Baseline; N=113,112,120) | 1.15 (1.02 to 1.3) | 1.16 (1.02 to 1.32) | 0.97 (0.85 to 1.09) | |
| 5/99 (11 moa; N=234,230,235) | 98 (78 to 124) | 50 (39 to 63) | 285 (225 to 363) | |
| NZ98/254 (Baseline; N=113,113,122) | 1.07 (0.99 to 1.15) | 1.04 (0.96 to 1.12) | 1 (0.93 to 1.07) | |
| NZ98/254 (11 moa; N=233,233,238) | 4.57 (3.66 to 5.71) | 2.68 (2.13 to 3.38) | 12 (9.79 to 15) | |
| M10713 (Baseline; N=84,64,88) | 2.36 (1.75 to 3.2) | 1.52 (1.07 to 2.17) | 1.29 (0.95 to 1.76) | |

| | | | | |
|--------------------------------|---------------------|---------------------|---------------------|--|
| M10713 (11 moa; N=199,177,188) | 2.55 (1.89 to 3.43) | 1.98 (1.45 to 2.71) | 3.62 (2.66 to 4.94) | |
|--------------------------------|---------------------|---------------------|---------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following 2 or 3-dose Primary Series and Booster Dose of Vaccination with rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following 2 or 3-dose Primary Series and Booster Dose of Vaccination with rMenB+OMV NZ ^[8] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of Geometric mean ELISA concentrations (GMCs) against N meningitidis serogroup B vaccine antigen 287-953, following 2 or 3 dose primary series and booster dose of rMenB+OMV NZ. Analysis was done on FAS-persistence and FAS-booster.

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

End point timeframe:

1 month after primary vaccination, pre-booster vaccination (persistence) and 1 month after booster 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 | B_2h3h5_11 | B_3h5_11 | B_68_11 | |
|---|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 218 | 225 | 221 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 1 month after primary vaccination (N=212,215,212) | 4688 (3884 to 5660) | 3152 (2594 to 3831) | 4682 (3850 to 5694) | |
| Pre-booster vaccination (N=213,220,215) | 474 (395 to 569) | 291 (241 to 351) | 1270 (1052 to 1533) | |
| 1 month after booster dose | 5900 (5047 to 6898) | 6062 (5150 to 7135) | 5898 (5016 to 6934) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 After a Two Dose Catch-up rMenB+OMV NZ Immunization Series in Children 2-10 Years of Age

| | |
|-----------------|--|
| End point title | Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 After a Two Dose Catch-up rMenB+OMV NZ Immunization Series in Children 2-10 Years of Age |
|-----------------|--|

End point description:

Immunogenicity was assessed in terms of Geometric mean ELISA concentrations (GMCs) against N meningitidis serogroup B vaccine antigen 287-953, after a two dose catch-up immunization series with rMenB+OMV NZ in children 2-10 years of age. Analysis was done on FAS-primary series.

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

End point timeframe:

1 month after second vaccination

| End point values | B_02 | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 389 | | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | 2333 (2124 to 2562) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 8 Against Serogroup C Following Concomitant Administration of rMenB +OMV NZ with MenC-CRM or MenC-CRM Alone

| | |
|-----------------|--|
| End point title | Percentages of Subjects with hSBA Titers ≥ 8 Against Serogroup C Following Concomitant Administration of rMenB +OMV NZ with MenC-CRM or MenC-CRM Alone ^[9] |
|-----------------|--|

End point description:

Non-inferiority of MenC-CRM was determined following co-administration of MenC-CRM and rMenB+OMV NZ or MenC-CRM alone at 3 and 5 months and booster dose at 12 months, as measured by the percentages of subjects achieving hSBA titers ≥ 8 against serogroup C. Analysis was done on PPS-primary series and PPS-booster.

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

End point timeframe:

Baseline, 1 month after second vaccination and 1 month after booster vaccination

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 | BC_35_12 | C_35_12 | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 85 | 72 | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Serogroup C (1 month after 2nd vacc) | 99 (94 to 100) | 100 (95 to 100) | | |
| Serogroup C (1 month after booster vacc; N=70,47) | 100 (95 to 100) | 100 (92 to 100) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | hSBA \geq 8; 1 month after 2nd vaccination |
| Statistical analysis description: Non-inferiority of MenC-CRM was determined following co-administration of MenC-CRM and rMenB+OMV NZ vs MenC-CRM control group at 1 month after 2nd vaccination for serogroup C. | |
| Comparison groups | BC_35_12 v C_35_12 |
| Number of subjects included in analysis | 157 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Vaccine group difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.4 |
| upper limit | 3.9 |

| | |
|--|--|
| Statistical analysis title | hSBA \geq 8; 1 month after booster vaccination |
| Statistical analysis description: Non-inferiority of MenC-CRM was determined following co-administration of MenC-CRM and rMenB+OMV NZ vs MenC-CRM control group at 1 month after booster vaccination for serogroup C. | |
| Comparison groups | BC_35_12 v C_35_12 |
| Number of subjects included in analysis | 157 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Method | Miettinen and Nurminen method |
| Parameter estimate | Vaccine group difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.2 |
| upper limit | 7.6 |

Secondary: GMTs Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM or MenC-CRM Alone

| | |
|-----------------|---|
| End point title | GMTs Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM or MenC-CRM Alone ^[10] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of GMTs against N meningitidis serogroup C strain following co-administration of MenC-CRM and rMenB+OMV NZ or MenC-CRM alone at 3 and 5 months and booster dose at 12 months. Analysis was done on FAS-primary series and FAS-booster.

End point type Secondary

End point timeframe:

1 month after second vaccination, 1 month after booster 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: There was no statistical null hypothesis associated with this immunogenicity objective.

| End point values | BC_35_12 | C_35_12 | | |
|--|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 102 | 88 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 1 month after 2nd vacc | 568 (461 to 701) | 905 (718 to 1141) | | |
| Pre-booster vacc (N=92,75) | 36 (28 to 47) | 56 (41 to 77) | | |
| 1 month after booster vacc (N=99,92) | 1201 (991 to 1456) | 1724 (1350 to 2201) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM or MenC-CRM Alone - Persistence

End point title GMTs Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM or MenC-CRM Alone - Persistence^[11]

End point description:

Immunogenicity was assessed in terms of GMTs against N meningitidis serogroup C strain following co-administration of MenC-CRM and rMenB+OMV NZ or MenC-CRM alone at 3 and 5 months and booster dose at 12 months. Analysis was done on FAS-persistence.

End point type Secondary

End point timeframe:

Pre-booster vaccination (persistence; 12 months of age)

Notes:

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

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

| End point values | BC_35_12 | C_35_12 | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 93 | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | 36 (28 to 46) | 56 (41 to 75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (M10713) and hSBA ≥ 8 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM

| | |
|-----------------|---|
| End point title | Percentages of Subjects with hSBA Titers ≥ 4 or hSBA Titers ≥ 5 (M10713) and hSBA ≥ 8 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM ^[12] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of percentages of subjects with hSBA titers ≥ 4 against N meningitidis serogroup B strains H44/76, 5/99, NZ98/254; hSBA titers ≥ 5 against strain M10713; hSBA titers ≥ 8 against strains H44/76, 5/99, NZ98/254, M10713; following co-administration of MenC-CRM and rMenB+OMV NZ at 3 and 5 months and a booster at 12 months. Analysis was done on FAS-primary series and FAS-booster.

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

End point timeframe:

1 month after second vaccination and 1 month after booster vaccination

Notes:

[12] - 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 | BC_35_12 | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 119 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| H44/76 (hSBA ≥ 4 ; 1 month after 2nd vacc) | 97 (92 to 99) | | | |
| H44/76 (hSBA ≥ 4 ; 1 month after booster vacc; N=114) | 100 (97 to 100) | | | |
| 5/99 (hSBA ≥ 4 ; 1 month after 2nd vacc) | 96 (90 to 99) | | | |
| 5/99 (hSBA ≥ 4 ; 1 month after booster vacc; N=113) | 97 (92 to 99) | | | |
| NZ98/254 (hSBA ≥ 4 ; 1 month after 2nd vacc; N=118) | 95 (89 to 98) | | | |
| NZ98/254 (hSBA ≥ 4 ; 1 mo after booster vacc; N=114) | 97 (93 to 99) | | | |
| M10713 (hSBA ≥ 5 ; 1 month after 2nd vacc; N=98) | 68 (58 to 77) | | | |
| M10713 (hSBA ≥ 5 ; 1 month after booster vacc; N=101) | 67 (57 to 76) | | | |
| H44/76 (hSBA ≥ 8 ; 1 month after 2nd vacc) | 97 (92 to 99) | | | |
| H44/76 (hSBA ≥ 8 ; 1 month after booster vacc; N=114) | 99 (95 to 100) | | | |
| 5/99 (hSBA ≥ 8 ; 1 month after 2nd vacc) | 96 (90 to 99) | | | |

| | | | | |
|---|---------------|--|--|--|
| 5/99 (hSBA \geq 8; 1 month after booster vacc; N=113) | 97 (92 to 99) | | | |
| NZ98/254 (hSBA \geq 8; 1 month after 2nd vacc; N=118) | 87 (80 to 93) | | | |
| NZ98/254 (hSBA \geq 8; 1 mo after booster vacc; N=114) | 95 (89 to 98) | | | |
| M10713 (hSBA \geq 8; 1 month after 2nd vacc; N=98) | 60 (50 to 70) | | | |
| M10713 (hSBA \geq 8; 1 month after booster vacc; N=101) | 61 (51 to 71) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs Against N. Meningitidis Serogroup B Strains Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM

| | |
|-----------------|---|
| End point title | GMTs Against N. Meningitidis Serogroup B Strains Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM ^[13] |
|-----------------|---|

End point description:

Immunogenicity was assessed in terms of GMTs against N meningitidis serogroup C strain following co-administration of MenC-CRM and rMenB+OMV NZ at 3 and 5 months and booster dose at 12 months. Analysis was done on FAS-persistence and FAS-booster.

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

End point timeframe:

1 month after second vaccination, pre-booster vaccination and 1 month after booster vaccination

Notes:

[13] - 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 | BC_35_12 | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 115 | | | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | | | | |
| H44/76 (1 month after 2nd vacc) | 226 (179 to 284) | | | |
| H44/76 (Pre-booster vacc) | 16 (13 to 20) | | | |
| H44/76 (1 month after booster vacc; N=114) | 239 (198 to 288) | | | |
| 5/99 (1 month after 2nd vacc) | 555 (409 to 753) | | | |
| 5/99 (Pre-booster vacc) | 55 (42 to 72) | | | |
| 5/99 (1 month after booster vacc; N=113) | 1623 (1210 to 2176) | | | |
| NZ98/254 (1 month after 2nd vacc; N=114) | 27 (21 to 34) | | | |
| NZ98/254 (Pre-booster vacc; N=115) | 2.63 (2.21 to 3.14) | | | |
| NZ98/254 (1 month after booster vacc; N=114) | 68 (54 to 86) | | | |

| | | | | |
|---|--------------------|--|--|--|
| M10713 (1 month after 2nd vacc; N=89) | 9.81 (7.06 to 14) | | | |
| M10713 (Pre-booster vacc; N=110) | 2.2 (1.72 to 2.82) | | | |
| M10713 (1 month after booster vacc; N=101) | 11 (7.72 to 15) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM

| | |
|-----------------|--|
| End point title | Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM ^[14] |
|-----------------|--|

End point description:

Immunogenicity was assessed in terms of Geometric mean ELISA concentrations against N meningitidis serogroup B vaccine antigen 287-953, following co-administration of MenC-CRM and rMenB+OMV NZ at 3 and 5 months and booster dose at 12 months. Analysis was done on FAS-primary and FAS-booster.

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

End point timeframe:

1 month after second vaccination, pre-booster vaccination and 1 month after booster vaccination

Notes:

[14] - 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 | BC_35_12 | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 116 | | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| 1 month after 2nd vacc | 2125 (1595 to 2830) | | | |
| Pre-booster vacc (N=111) | 194 (164 to 230) | | | |
| 1 month after booster vacc (N=113) | 4281 (3411 to 5372) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM - Persistence

| | |
|-----------------|--|
| End point title | Geometric Mean ELISA Concentrations Against Vaccine Antigen 287-953 Following Concomitant Administration of rMenB+OMV NZ with MenC-CRM - Persistence ^[15] |
|-----------------|--|

End point description:

Immunogenicity was assessed in terms of GMTs against Geometric mean ELISA concentrations against N meningitidis serogroup B vaccine antigen 287-953, following co-administration of MenC-CRM and rMenB+OMV NZ at 3 and 5 months and booster dose at 12 months. Analysis was done on FAS-persistence.

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

End point timeframe:

Pre-booster vaccination (persistence; 12 months of age)

Notes:

[15] - 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 | BC_35_12 | | | |
|--|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 115 | | | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | 196 (166 to 231) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Reported Immediate Reactions within 30 Minutes after any Vaccination with rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Number of Subjects who Reported Immediate Reactions within 30 Minutes after any Vaccination with rMenB+OMV NZ |
|-----------------|---|

End point description:

Safety was assessed in terms of number of subjects who reported immediate reactions within 30 minutes following a 4-dose regimen (2.5, 3.5, 5 and 11 months) or a 3-dose regimen (3.5, 5 and 11 months or 6, 8 and 11 months) of rMenB+OMV NZ. Analysis was done on solicited safety set.

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

End point timeframe:

Within 30 minutes after any vaccination

| End point values | B_2h3h5_11b | B_3h5_11b | B_68_11b | |
|-----------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 252 | 249 | 250 | |
| Units: Subjects | | | | |
| Tenderness | 13 | 9 | 9 | |
| Erythema | 19 | 19 | 7 | |
| Induration | 4 | 3 | 2 | |
| Swelling | 1 | 2 | 1 | |
| Change in eating habits | 0 | 2 | 1 | |
| Sleepiness | 1 | 2 | 3 | |
| Unusual crying | 4 | 3 | 4 | |
| Vomiting | 1 | 0 | 0 | |

| | | | | |
|--|---|---|---|--|
| Diarrhea | 0 | 0 | 1 | |
| Irritability | 1 | 2 | 1 | |
| Rash | 0 | 1 | 1 | |
| Fever ($\geq 38^{\circ}\text{C}$) | 3 | 2 | 2 | |
| Medic. used for pain (N=252,248,250) | 0 | 0 | 0 | |
| Medically-attended fever | 0 | 0 | 0 | |
| Medic. used to treat high temp. (N=252,248,250) | 1 | 1 | 0 | |
| Medic. used to prevent high temp. (N=252,248,250) | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Solicited Local and Systemic Adverse Events (AEs) Following a 3 or 4-dose Regimen of rMenB+OMV NZ

| | |
|-----------------|---|
| End point title | Number of Subjects with Solicited Local and Systemic Adverse Events (AEs) Following a 3 or 4-dose Regimen of rMenB+OMV NZ ^[16] |
|-----------------|---|

End point description:

Safety was assessed in terms of number of subjects with solicited local and systemic AEs after any vaccination following a 4-dose regimen (2.5, 3.5, 5 and 11 months) or as a 3-dose regimen (3.5, 5 and 11 months or 6, 8 and 11 months) of rMenB+OMV NZ. Analysis was done on solicited safety set.

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

End point timeframe:

Day 1 to day 7 after any vaccination

Notes:

[16] - 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: All safety analyses were run in the safety population.

| End point values | B_2h3h5_11 | B_3h5_11 | B_68_11 | |
|---|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 247 | 243 | 246 | |
| Units: Subjects | | | | |
| Any local (N=245,241,244) | 226 | 213 | 202 | |
| Tenderness (N=245,241,244) | 200 | 174 | 166 | |
| Erythema (N=245,241,244) | 164 | 156 | 157 | |
| Induration (N=245,241,244) | 161 | 117 | 121 | |
| Swelling (N=245,241,244) | 120 | 75 | 84 | |
| Any systemic (N=245,241,244) | 238 | 236 | 233 | |
| Change in eating habits (N=245,241,244) | 141 | 112 | 121 | |
| Sleepiness (N=245,241,244) | 186 | 152 | 143 | |
| Irritability (N=245,241,244) | 180 | 156 | 151 | |
| Vomiting (N=245,241,244) | 65 | 39 | 55 | |
| Diarrhea (N=245,241,244) | 91 | 69 | 74 | |
| Rash (N=245,241,244) | 23 | 21 | 22 | |
| Unusual Crying (N=245,241,244) | 198 | 186 | 156 | |
| Fever ($\geq 38^{\circ}\text{C}$) (N=245,241,244) | 197 | 189 | 184 | |

| | | | | |
|--|-----|-----|-----|--|
| Medic. used for pain (N=245,241,244) | 129 | 110 | 109 | |
| Medic. used to prevent high temp. (N=245,241,244) | 97 | 94 | 99 | |
| Medic. used to treat high temp. (N=245,242,244) | 193 | 186 | 177 | |
| Medically-attended fever | 16 | 10 | 15 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Reported Immediate Reactions within 30 Minutes After Any Vaccination - Groups B_02_2_5 and B_02_6_10

| | |
|-----------------|---|
| End point title | Number of Subjects who Reported Immediate Reactions within 30 Minutes After Any Vaccination - Groups B_02_2_5 and B_02_6_10 ^[17] |
|-----------------|---|

End point description:

Safety was assessed in terms of number of subjects with solicited local and systemic AEs after any vaccination in subjects aged 2 - 10 years who received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Analysis was done on solicited safety set.

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

End point timeframe:

Within 30 minutes after any vaccination

Notes:

[17] - 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 | B_02_2_5 | B_02_6_10 | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 300 | | |
| Units: Subjects | | | | |
| Pain | 6 | 17 | | |
| Erythema | 6 | 2 | | |
| Induration | 1 | 3 | | |
| Swelling | 2 | 2 | | |
| Chills (N=0,300) | 0 | 2 | | |
| Change in eating habits (N=104,0) | 0 | 0 | | |
| Sleepiness (N=104,0) | 0 | 0 | | |
| Irritability (N=104,0) | 1 | 0 | | |
| Vomiting (N=104,0) | 0 | 0 | | |
| Nausea (N=0,300) | 0 | 2 | | |
| Malaise (N=0,300) | 0 | 4 | | |
| Diarrhoea (N=104,0) | 0 | 0 | | |
| Headache | 0 | 1 | | |
| Rash | 0 | 0 | | |
| Arthralgia | 0 | 1 | | |
| Myalgia (N=0,300) | 0 | 5 | | |
| Fever ($\geq 38^{\circ}\text{C}$) | 0 | 0 | | |
| Medic. used for pain | 0 | 1 | | |

| | | | | |
|-----------------------------------|---|---|--|--|
| Medic. used to prevent high temp. | 0 | 1 | | |
| Medic. used to treat high temp. | 0 | 0 | | |
| Medically-attended fever | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Solicited Local and Systemic AEs in Groups B_02_2_5 and B_02_6_10

| | |
|---|---|
| End point title | Number of Subjects with Solicited Local and Systemic AEs in Groups B_02_2_5 and B_02_6_10 |
| End point description: | |
| Safety was assessed in terms of number of subjects with solicited local and systemic AEs after any vaccination in subjects aged 2- 10 years who received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Analysis was done on solicited safety set. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to day 7 after any vaccination | |

| End point values | B_02_2_5 | B_02_6_10 | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 102 | 299 | | |
| Units: Subjects | | | | |
| Any Local (N=100,297) | 99 | 287 | | |
| Pain (N=100,297) | 98 | 287 | | |
| Erythema (N=100,297) | 58 | 179 | | |
| Induration (N=100,297) | 41 | 123 | | |
| Swelling (N=100,297) | 50 | 146 | | |
| Any systemic (N=100,297) | 78 | 205 | | |
| Chills (N=0,296) | 0 | 45 | | |
| Change in eating habits (N=100,0) | 35 | 0 | | |
| Sleepiness (N=100,0) | 39 | 0 | | |
| Irritability (N=100,0) | 49 | 0 | | |
| Malaise (N=0,296) | 0 | 114 | | |
| Vomiting (N=100,0) | 7 | 0 | | |
| Nausea (N=0,296) | 0 | 36 | | |
| Diarrhoea (N=100,0) | 12 | 0 | | |
| Headache (N=100,296) | 7 | 89 | | |
| Rash (N=100,296) | 9 | 20 | | |
| Arthralgia (N=100,296) | 35 | 49 | | |
| Myalgia (N=0,296) | 0 | 126 | | |
| Fever ($\geq 38^{\circ}\text{C}$) (N=100,296) | 20 | 41 | | |
| Medic. used for pain (N=100,296) | 48 | 158 | | |
| Medic. used to prevent high temp. (N=100,296) | 7 | 44 | | |
| Medic. used to treat high temp. (N=100,296) | 20 | 54 | | |

| | | | | |
|--------------------------|---|---|--|--|
| Medically-attended fever | 0 | 7 | | |
|--------------------------|---|---|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who Reported Immediate Reactions Within 30 Minutes After Any rMenB+OMV NZ or MenC-CRM Vaccination

| | |
|-----------------|--|
| End point title | Number of Subjects who Reported Immediate Reactions Within 30 Minutes After Any rMenB+OMV NZ or MenC-CRM Vaccination ^[18] |
|-----------------|--|

End point description:

Safety was assessed in terms of number of subjects with solicited local and systemic AEs after any vaccination with rMenB+OMV NZ or MenC-CRM. Analysis was done on solicited safety set.

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

End point timeframe:

Within 30 minutes after any vaccination

Notes:

[18] - 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: All safety analyses were run in the safety population.

| End point values | BC_35_12 | C_35_12 | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 126 | 124 | | |
| Units: Subjects | | | | |
| Tenderness (rMenB+OMV NZ) (N=126,0) | 7 | 0 | | |
| Erythema (rMenB+OMV NZ) (N=126,0) | 3 | 0 | | |
| Induration (rMenB+OMV NZ) (N=126,0) | 1 | 0 | | |
| Swelling (rMenB+OMV NZ) (N=126,0) | 0 | 0 | | |
| Tenderness (MenC-CRM) | 5 | 5 | | |
| Erythema (MenC-CRM) | 4 | 5 | | |
| Induration (MenC-CRM) | 0 | 0 | | |
| Swelling (MenC-CRM) | 0 | 0 | | |
| Change in eating habits | 0 | 0 | | |
| Sleepiness | 0 | 0 | | |
| Unusual crying | 0 | 0 | | |
| Irritability | 0 | 0 | | |
| Vomiting | 1 | 0 | | |
| Diarrhea | 0 | 0 | | |
| Rash | 0 | 0 | | |
| Fever ($\geq 38^{\circ}\text{C}$) | 1 | 0 | | |
| Medic. used for pain | 0 | 0 | | |
| Medic. used to prevent high temp. | 0 | 0 | | |
| Medic. used to treat high temp. | 0 | 0 | | |
| Medically-attended fever | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Solicited Local and Systemic AEs in Groups BC_35_12 and C_35_12 after any rMenB+OMV NZ or MenC-CRM Vaccination

| | |
|-----------------|--|
| End point title | Number of Subjects with Solicited Local and Systemic AEs in Groups BC_35_12 and C_35_12 after any rMenB+OMV NZ or MenC-CRM Vaccination ^[19] |
|-----------------|--|

End point description:

Safety was assessed in terms of number of subjects with solicited local and systemic AEs after any vaccination with rMenB+OMV NZ or MenC-CRM. Analysis was done on solicited safety set.

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

End point timeframe:

Day 1 to day 7 after any vaccination

Notes:

[19] - 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: All safety analyses were run in the safety population.

| End point values | BC_35_12 | C_35_12 | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 117 | | |
| Units: Subjects | | | | |
| Any local rMenB + OMZ NV | 107 | 0 | | |
| Any local MenC-CRM | 104 | 79 | | |
| Any systemic | 123 | 106 | | |
| Tenderness (rMenB+OMV NZ) (N=123,0) | 105 | 0 | | |
| Erythema (rMenB+OMV NZ) (N=123,0) | 48 | 0 | | |
| Induration (rMenB+OMV NZ) (N=123,0) | 37 | 0 | | |
| Swelling (rMenB+OMV NZ) (N=123,0) | 21 | 0 | | |
| Tenderness (MenC-CRM) (N=123,117) | 104 | 74 | | |
| Erythema (MenC-CRM) (N=123,117) | 25 | 24 | | |
| Induration (MenC-CRM) (N=123,117) | 10 | 26 | | |
| Swelling (MenC-CRM) (N=123,117) | 12 | 21 | | |
| Change in eating habits (N=123,117) | 67 | 47 | | |
| Sleepiness (N=123,117) | 93 | 78 | | |
| Unusual crying (N=123,117) | 105 | 87 | | |
| Irritability (N=123,117) | 95 | 66 | | |
| Vomiting (N=123,117) | 29 | 27 | | |
| Diarrhea (N=123,117) | 41 | 40 | | |
| Rash (N=123,117) | 8 | 4 | | |
| Fever ($\geq 38^{\circ}\text{C}$) (N=123,117) | 97 | 45 | | |
| Medic. used for pain (N=123,117) | 102 | 69 | | |
| Medic. used to prevent high temp. | 49 | 25 | | |

| | | | | |
|---------------------------------|----|----|--|--|
| Medic. used to treat high temp. | 90 | 40 | | |
| Medically-attended fever | 7 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Groups B_2h3h5_11, B_3h5_11 and B_68_11

| | |
|-----------------|---|
| End point title | Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Groups B_2h3h5_11, B_3h5_11 and B_68_11 |
|-----------------|---|

End point description:

Safety was assessed in terms of number of subjects reporting any unsolicited AEs (day 1-7 after any vaccination), serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal from the study (collected throughout the study period) following any vaccination with rMenB+OMV. Analysis was done on unsolicited safety set.

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

End point timeframe:

Until 12 months of age; Day 1 to day 7 (All AEs)

| End point values | B_2h3h5_11b | B_3h5_11b | B_68_11b | |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 252 | 249 | 250 | |
| Units: Subjects | | | | |
| All AEs (days 1-7) | 200 | 186 | 196 | |
| At least possible related AEs | 88 | 41 | 62 | |
| SAEs | 15 | 18 | 9 | |
| At least possibly related SAEs | 1 | 1 | 1 | |
| Medically attended AEs | 178 | 179 | 182 | |
| AEs leading to premature withdrawal | 1 | 1 | 0 | |
| Deaths | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Groups B_02_2_5 and B_02_6_10

| | |
|-----------------|---|
| End point title | Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Groups B_02_2_5 and B_02_6_10 ^[20] |
|-----------------|---|

End point description:

Safety was assessed in terms of number of subjects reporting any unsolicited AEs (day 1-7 after any vaccination), serious adverse events (SAEs), medically attended AEs, AEs leading to premature

withdrawal from the study (collected throughout the study period) following any vaccination with rMenB+OMV NZ. Analysis was done on unsolicited safety set.

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

End point timeframe:

Day 1 to Day 7 (All AEs). Throughout the study period (SAEs, medically attended or leading to premature withdrawal AEs)

Notes:

[20] - 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: All safety analyses were run in the safety population.

| End point values | B_02_2_5 | B_02_6_10 | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 300 | | |
| Units: Subjects | | | | |
| All AEs (days 1-7) | 58 | 101 | | |
| At least possible related AEs | 16 | 24 | | |
| SAEs | 1 | 2 | | |
| At least possibly related SAEs | 0 | 0 | | |
| Medically attended AEs | 42 | 74 | | |
| AEs leading to premature withdrawal | 0 | 0 | | |
| Deaths | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Group BC_35_12 and C_35_12

| | |
|-----------------|--|
| End point title | Number of Subjects Reporting Unsolicited AEs Following Any Vaccination with rMenB+OMV NZ in Group BC_35_12 and C_35_12 ^[21] |
|-----------------|--|

End point description:

Safety was assessed in terms of number of subjects reporting any unsolicited AEs (day 1-7 after any vaccination), serious adverse events (SAEs), medically attended AEs, AEs leading to premature withdrawal from the study (collected throughout the study period) following any vaccination with rMenB+OMV NZ or MenC-CRM. Analysis was done on unsolicited safety set.

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

End point timeframe:

Day 1 to Day 301 for BC_35_12 and C_35_12, Day 302 to Day 391 for C_35_12; Day 1 to day 7 (All AEs)

Notes:

[21] - 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: All safety analyses were run in the safety population.

| End point values | BC_35_12 | C_35_12 | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 126 | 123 | | |
| Units: Subjects | | | | |
| All AEs (days 1-7) | 103 | 90 | | |
| At least possibly related AEs | 14 | 12 | | |
| SAEs | 5 | 7 | | |
| At least possibly related SAEs | 0 | 0 | | |
| Medically attended AEs | 99 | 85 | | |
| AEs leading to premature withdrawal | 0 | 0 | | |
| Deaths | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 months of age for groups B_2h3h5_11, B_3h5_11 and B_68_11; Day 1 to Day 91 for groups B02_2_5 and B02_6_10; Day 1 to Day 301 for group BC_35_12; Day 1 to Day 391 for group C_35_12

Adverse event reporting additional description:

All solicited AEs were collected by systematic assessment and unsolicited AEs were collected by non-systematic assessment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | B_68_11 |
|-----------------------|---------|

Reporting group description:

Subjects, approximately 6 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 6 and 8 months of age, followed by a booster dose at 11 months of age.

| | |
|-----------------------|----------|
| Reporting group title | B_3h5_11 |
|-----------------------|----------|

Reporting group description:

Subjects, approximately 3.5 months of age received 2 dose primary vaccination of rMenB+OMV NZ at 3.5 and 5 months of age, followed by a booster dose at 11 months of age.

| | |
|-----------------------|------------|
| Reporting group title | B_2h3h5_11 |
|-----------------------|------------|

Reporting group description:

Subjects, approximately 2.5 months of age received 3 dose primary vaccination of rMenB+OMV NZ at 2.5, 3.5, 5 months of age, followed by a booster dose at 11 months of age

| | |
|-----------------------|---------|
| Reporting group title | C_35_12 |
|-----------------------|---------|

Reporting group description:

Subjects, 3 months of age received MenCCRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone at 7 months of age and rMenB+OMV NZ alone at 13 and 15 months of age.

| | |
|-----------------------|----------|
| Reporting group title | BC_35_12 |
|-----------------------|----------|

Reporting group description:

Subjects, 3 months of age received rMenB+OMV NZ + MenC-CRM and Synflorix concomitantly at 3, 5 and 12 months of age and an additional dose of Synflorix alone dose at 7 months of age

| | |
|-----------------------|-----------|
| Reporting group title | B_02_6_10 |
|-----------------------|-----------|

Reporting group description:

Subjects, 6-10 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start.

| | |
|-----------------------|----------|
| Reporting group title | B_02_2_5 |
|-----------------------|----------|

Reporting group description:

Subjects, 2-5 years of age received 2 catch-up doses of rMenB+OMV NZ, each at 0 and 2 months. Blood draw at 0 and 3 months since study start.

| Serious adverse events | B_68_11 | B_3h5_11 | B_2h3h5_11 |
|---|-----------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 250 (3.60%) | 18 / 249 (7.23%) | 15 / 252 (5.95%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FALL | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| CONGENITAL CENTRAL NERVOUS SYSTEM ANOMALY | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (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 |
| Nervous system disorders | | | |
| BENIGN INTRACRANIAL HYPERTENSION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE CONVULSION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GENERALISED TONIC-CLONIC SEIZURE | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 2 / 249 (0.80%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LYMPHADENOPATHY | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 0 / 249 (0.00%) | 0 / 252 (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 | 1 / 250 (0.40%) | 2 / 249 (0.80%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| GLAUCOMA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ALLERGIC COLITIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOOD POISONING | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INGUINAL HERNIA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ADENOIDAL HYPERTROPHY | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 2 / 250 (0.80%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOKING | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| SLEEP APNOEA SYNDROME | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TONSILLAR HYPERTROPHY | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WHEEZING | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| Renal and urinary disorders | | | |
| HYDRONEPHROSIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| JUVENILE IDIOPATHIC ARTHRITIS | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHIOLITIS | | | |
| subjects affected / exposed | 3 / 250 (1.20%) | 2 / 249 (0.80%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 2 / 249 (0.80%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHOPNEUMONIA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| EAR INFECTION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 / 250 (0.80%) | 4 / 249 (1.61%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS ROTAVIRUS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS SALMONELLA | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| LARYNGITIS | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 0 / 249 (0.00%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| MASTOIDITIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORAL CANDIDIASIS | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 2 / 249 (0.80%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 2 / 252 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION VIRAL | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SALMONELLOSIS | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 250 (0.40%) | 0 / 249 (0.00%) | 0 / 252 (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 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| COW'S MILK INTOLERANCE | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 1 / 249 (0.40%) | 0 / 252 (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 |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 3 / 249 (1.20%) | 1 / 252 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | C_35_12 | BC_35_12 | B_02_6_10 |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 123 (6.50%) | 5 / 126 (3.97%) | 2 / 300 (0.67%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FALL | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| CONGENITAL CENTRAL NERVOUS SYSTEM ANOMALY | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| BENIGN INTRACRANIAL HYPERTENSION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEBRILE CONVULSION | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (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 |
| GENERALISED TONIC-CLONIC SEIZURE | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (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 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LYMPHADENOPATHY | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 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 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| GLAUCOMA | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (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 |
| Gastrointestinal disorders | | | |
| ALLERGIC COLITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOOD POISONING | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 1 / 300 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INGUINAL HERNIA | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOMITING | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| ADENOIDAL HYPERTROPHY | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| CHOKING | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SLEEP APNOEA SYNDROME | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TONSILLAR HYPERTROPHY | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WHEEZING | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 126 (0.79%) | 0 / 300 (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 |
| Renal and urinary disorders | | | |
| HYDRONEPHROSIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| JUVENILE IDIOPATHIC ARTHRITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| ATYPICAL PNEUMONIA | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 126 (0.79%) | 0 / 300 (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 / 123 (0.81%) | 2 / 126 (1.59%) | 0 / 300 (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 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHOPNEUMONIA | | | |
| subjects affected / exposed | 3 / 123 (2.44%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EAR INFECTION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS ROTAVIRUS | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 1 / 126 (0.79%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS SALMONELLA | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARYNGITIS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MASTOIDITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 1 / 126 (0.79%) | 0 / 300 (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 |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 2 / 126 (1.59%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION VIRAL | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SALMONELLOSIS | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| COW'S MILK INTOLERANCE | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 0 / 300 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEHYDRATION | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 0 / 126 (0.00%) | 0 / 300 (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 |

| | | | |
|---|-----------------|--|--|
| Serious adverse events | B_02_2_5 | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| CONCUSSION | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FALL | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKULL FRACTURE | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| CONGENITAL CENTRAL NERVOUS SYSTEM ANOMALY | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| BENIGN INTRACRANIAL HYPERTENSION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FEBRILE CONVULSION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GENERALISED TONIC-CLONIC SEIZURE | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LYMPHADENOPATHY | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| GLAUCOMA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| ALLERGIC COLITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FOOD POISONING | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INGUINAL HERNIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VOMITING | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ADENOIDAL HYPERTROPHY | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOKING | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SLEEP APNOEA SYNDROME | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TONSILLAR HYPERTROPHY | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| WHEEZING | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| HYDRONEPHROSIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| JUVENILE IDIOPATHIC ARTHRITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHIOLITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHOPNEUMONIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| EAR INFECTION | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROENTERITIS | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROENTERITIS ROTAVIRUS | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROENTERITIS SALMONELLA | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LARYNGITIS | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOWER RESPIRATORY TRACT INFECTION | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MASTOIDITIS | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| NASOPHARYNGITIS | | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ORAL CANDIDIASIS | | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY TRACT INFECTION VIRAL | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SALMONELLOSIS | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|-----------------|--|--|
| COW'S MILK INTOLERANCE | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | B_68_11 | B_3h5_11 | B_2h3h5_11 |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 245 / 250 (98.00%) | 240 / 249 (96.39%) | 246 / 252 (97.62%) |
| Nervous system disorders | | | |
| HEADACHE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| SOMNOLENCE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 144 / 250 (57.60%) | 152 / 249 (61.04%) | 186 / 252 (73.81%) |
| occurrences (all) | 256 | 296 | 450 |
| General disorders and administration site conditions | | | |
| CHILLS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CRYING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 157 / 250 (62.80%) | 186 / 249 (74.70%) | 198 / 252 (78.57%) |
| occurrences (all) | 333 | 350 | 554 |
| INDURATION | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed | 27 / 250 (10.80%) | 23 / 249 (9.24%) | 58 / 252 (23.02%) |
| occurrences (all) | 42 | 33 | 101 |
| INJECTION SITE ERYTHEMA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 157 / 250 (62.80%) | 160 / 249 (64.26%) | 169 / 252 (67.06%) |
| occurrences (all) | 314 | 312 | 427 |
| INJECTION SITE INDURATION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 122 / 250 (48.80%) | 118 / 249 (47.39%) | 162 / 252 (64.29%) |
| occurrences (all) | 227 | 209 | 382 |
| INJECTION SITE PAIN | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 168 / 250 (67.20%) | 175 / 249 (70.28%) | 202 / 252 (80.16%) |
| occurrences (all) | 348 | 340 | 505 |
| INJECTION SITE SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 84 / 250 (33.60%) | 76 / 249 (30.52%) | 120 / 252 (47.62%) |
| occurrences (all) | 137 | 110 | 237 |
| MALAISE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| PYREXIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 189 / 250 (75.60%) | 192 / 249 (77.11%) | 201 / 252 (79.76%) |
| occurrences (all) | 429 | 403 | 505 |
| SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 19 / 250 (7.60%) | 6 / 249 (2.41%) | 26 / 252 (10.32%) |
| occurrences (all) | 20 | 6 | 36 |
| Gastrointestinal disorders | | | |
| DIARRHOEA | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 76 / 250 (30.40%) | 74 / 249 (29.72%) | 96 / 252 (38.10%) |
| occurrences (all) | 134 | 108 | 172 |
| NAUSEA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 250 (0.00%) | 0 / 249 (0.00%) | 0 / 252 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| VOMITING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 58 / 250 (23.20%) | 46 / 249 (18.47%) | 69 / 252 (27.38%) |
| occurrences (all) | 93 | 60 | 110 |
| Respiratory, thoracic and mediastinal disorders | | | |
| BRONCHOSPASM | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 250 (1.20%) | 5 / 249 (2.01%) | 3 / 252 (1.19%) |
| occurrences (all) | 5 | 5 | 4 |
| CATARRH | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 14 / 250 (5.60%) | 14 / 249 (5.62%) | 8 / 252 (3.17%) |
| occurrences (all) | 19 | 15 | 14 |
| COUGH | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 13 / 250 (5.20%) | 6 / 249 (2.41%) | 12 / 252 (4.76%) |
| occurrences (all) | 18 | 6 | 15 |
| Skin and subcutaneous tissue disorders | | | |
| ERYTHEMA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 12 / 250 (4.80%) | 8 / 249 (3.21%) | 20 / 252 (7.94%) |
| occurrences (all) | 18 | 11 | 29 |
| RASH | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 32 / 250 (12.80%) | 28 / 249 (11.24%) | 36 / 252 (14.29%) |
| occurrences (all) | 42 | 31 | 51 |
| Psychiatric disorders | | | |

| | | | |
|---|---------------------------|---------------------------|---------------------------|
| EATING DISORDER alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 121 / 250 (48.40%) 242 | 112 / 249 (44.98%) 188 | 141 / 252 (55.95%) 302 |
| IRRITABILITY alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 153 / 250 (61.20%) 317 | 156 / 249 (62.65%) 312 | 181 / 252 (71.83%) 478 |
| Musculoskeletal and connective tissue disorders ARTHRALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 250 (0.00%) 0 | 0 / 249 (0.00%) 0 | 0 / 252 (0.00%) 0 |
| MYALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 250 (0.00%) 0 | 0 / 249 (0.00%) 0 | 0 / 252 (0.00%) 0 |
| Infections and infestations BRONCHIOLITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 13 / 250 (5.20%) 14 | 26 / 249 (10.44%) 29 | 18 / 252 (7.14%) 26 |
| BRONCHITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 33 / 250 (13.20%) 51 | 36 / 249 (14.46%) 53 | 37 / 252 (14.68%) 54 |
| BRONCHOPNEUMONIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 250 (0.40%) 1 | 2 / 249 (0.80%) 2 | 0 / 252 (0.00%) 0 |
| CONJUNCTIVITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 17 / 250 (6.80%) 19 | 15 / 249 (6.02%) 16 | 27 / 252 (10.71%) 30 |
| EAR INFECTION | | | |

| | | | |
|--|-------------------|-------------------|-------------------|
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 16 / 250 (6.40%) | 9 / 249 (3.61%) | 12 / 252 (4.76%) |
| occurrences (all) | 21 | 9 | 13 |
| GASTROENTERITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 32 / 250 (12.80%) | 23 / 249 (9.24%) | 25 / 252 (9.92%) |
| occurrences (all) | 37 | 25 | 31 |
| INFLUENZA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 250 (2.00%) | 4 / 249 (1.61%) | 7 / 252 (2.78%) |
| occurrences (all) | 6 | 5 | 8 |
| LARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 15 / 250 (6.00%) | 5 / 249 (2.01%) | 12 / 252 (4.76%) |
| occurrences (all) | 17 | 5 | 12 |
| NASOPHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 47 / 250 (18.80%) | 31 / 249 (12.45%) | 38 / 252 (15.08%) |
| occurrences (all) | 71 | 55 | 73 |
| OTITIS MEDIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 14 / 250 (5.60%) | 4 / 249 (1.61%) | 7 / 252 (2.78%) |
| occurrences (all) | 17 | 4 | 9 |
| OTITIS MEDIA ACUTE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 14 / 250 (5.60%) | 8 / 249 (3.21%) | 10 / 252 (3.97%) |
| occurrences (all) | 15 | 10 | 12 |
| PHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 14 / 250 (5.60%) | 10 / 249 (4.02%) | 11 / 252 (4.37%) |
| occurrences (all) | 16 | 12 | 12 |
| RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|-------------------|-------------------|-------------------|
| subjects affected / exposed | 28 / 250 (11.20%) | 14 / 249 (5.62%) | 18 / 252 (7.14%) |
| occurrences (all) | 37 | 26 | 30 |
| TONSILLITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 7 / 250 (2.80%) | 3 / 249 (1.20%) | 6 / 252 (2.38%) |
| occurrences (all) | 10 | 3 | 7 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 54 / 250 (21.60%) | 56 / 249 (22.49%) | 49 / 252 (19.44%) |
| occurrences (all) | 79 | 86 | 67 |
| VIRAL INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 14 / 250 (5.60%) | 26 / 249 (10.44%) | 16 / 252 (6.35%) |
| occurrences (all) | 15 | 32 | 21 |

| Non-serious adverse events | C_35_12 | BC_35_12 | B_02_6_10 |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 115 / 123 (93.50%) | 124 / 126 (98.41%) | 288 / 300 (96.00%) |
| Nervous system disorders | | | |
| HEADACHE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 90 / 300 (30.00%) |
| occurrences (all) | 0 | 0 | 124 |
| SOMNOLENCE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 84 / 123 (68.29%) | 93 / 126 (73.81%) | 0 / 300 (0.00%) |
| occurrences (all) | 233 | 214 | 0 |
| General disorders and administration site conditions | | | |
| CHILLS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 47 / 300 (15.67%) |
| occurrences (all) | 0 | 0 | 51 |
| CRYING | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed | 93 / 123 (75.61%) | 105 / 126 (83.33%) | 0 / 300 (0.00%) |
| occurrences (all) | 289 | 271 | 0 |
| INDURATION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 123 (0.81%) | 1 / 126 (0.79%) | 6 / 300 (2.00%) |
| occurrences (all) | 1 | 1 | 6 |
| INJECTION SITE ERYTHEMA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 41 / 123 (33.33%) | 62 / 126 (49.21%) | 180 / 300 (60.00%) |
| occurrences (all) | 142 | 197 | 272 |
| INJECTION SITE INDURATION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 41 / 123 (33.33%) | 42 / 126 (33.33%) | 124 / 300 (41.33%) |
| occurrences (all) | 107 | 107 | 173 |
| INJECTION SITE PAIN | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 102 / 123 (82.93%) | 114 / 126 (90.48%) | 287 / 300 (95.67%) |
| occurrences (all) | 469 | 685 | 537 |
| INJECTION SITE SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 35 / 123 (28.46%) | 34 / 126 (26.98%) | 146 / 300 (48.67%) |
| occurrences (all) | 96 | 76 | 218 |
| MALAISE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 117 / 300 (39.00%) |
| occurrences (all) | 0 | 0 | 160 |
| PYREXIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 77 / 123 (62.60%) | 99 / 126 (78.57%) | 47 / 300 (15.67%) |
| occurrences (all) | 162 | 195 | 56 |
| SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 4 / 300 (1.33%) |
| occurrences (all) | 0 | 0 | 4 |

| | | | |
|---|-------------------|-------------------|-------------------|
| Gastrointestinal disorders DIARRHOEA alternative assessment type: Systematic subjects affected / exposed occurrences (all) NAUSEA alternative assessment type: Systematic subjects affected / exposed occurrences (all) VOMITING alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 49 / 123 (39.84%) | 41 / 126 (32.54%) | 5 / 300 (1.67%) |
| | 99 | 61 | 5 |
| | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 38 / 300 (12.67%) |
| | 0 | 0 | 44 |
| | 31 / 123 (25.20%) | 30 / 126 (23.81%) | 6 / 300 (2.00%) |
| | 48 | 44 | 6 |
| | | | |
| | | | |
| | | | |
| Respiratory, thoracic and mediastinal disorders BRONCHOSPASM alternative assessment type: Systematic subjects affected / exposed occurrences (all) CATARRH alternative assessment type: Systematic subjects affected / exposed occurrences (all) COUGH alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 7 / 123 (5.69%) | 8 / 126 (6.35%) | 0 / 300 (0.00%) |
| | 13 | 9 | 0 |
| | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 2 / 300 (0.67%) |
| | 0 | 0 | 2 |
| | 1 / 123 (0.81%) | 1 / 126 (0.79%) | 5 / 300 (1.67%) |
| | 1 | 1 | 5 |
| | | | |
| | | | |
| | | | |
| Skin and subcutaneous tissue disorders ERYTHEMA alternative assessment type: Systematic subjects affected / exposed occurrences (all) RASH alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 123 (0.00%) | 2 / 126 (1.59%) | 3 / 300 (1.00%) |
| | 0 | 2 | 4 |
| | 6 / 123 (4.88%) | 11 / 126 (8.73%) | 21 / 300 (7.00%) |
| | 7 | 13 | 23 |
| | | | |
| | | | |

| | | | |
|---|--------------------------|--------------------------|---------------------------|
| Psychiatric disorders EATING DISORDER alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 64 / 123 (52.03%) 145 | 67 / 126 (53.17%) 119 | 0 / 300 (0.00%) 0 |
| IRRITABILITY alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 79 / 123 (64.23%) 231 | 95 / 126 (75.40%) 237 | 1 / 300 (0.33%) 1 |
| Musculoskeletal and connective tissue disorders ARTHRALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 123 (0.00%) 0 | 0 / 126 (0.00%) 0 | 50 / 300 (16.67%) 63 |
| MYALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 123 (0.00%) 0 | 0 / 126 (0.00%) 0 | 127 / 300 (42.33%) 169 |
| Infections and infestations BRONCHIOLITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 5 / 123 (4.07%) 5 | 6 / 126 (4.76%) 6 | 0 / 300 (0.00%) 0 |
| BRONCHITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 123 (2.44%) 3 | 0 / 126 (0.00%) 0 | 7 / 300 (2.33%) 7 |
| BRONCHOPNEUMONIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 9 / 123 (7.32%) 11 | 6 / 126 (4.76%) 8 | 0 / 300 (0.00%) 0 |
| CONJUNCTIVITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 123 (2.44%) 3 | 2 / 126 (1.59%) 2 | 1 / 300 (0.33%) 1 |

| | | | |
|--|-------------------|-------------------|-----------------|
| EAR INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 123 (4.07%) | 1 / 126 (0.79%) | 0 / 300 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| GASTROENTERITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 123 (4.88%) | 5 / 126 (3.97%) | 3 / 300 (1.00%) |
| occurrences (all) | 6 | 6 | 3 |
| INFLUENZA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 123 (1.63%) | 7 / 126 (5.56%) | 3 / 300 (1.00%) |
| occurrences (all) | 2 | 7 | 3 |
| LARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 3 / 126 (2.38%) | 0 / 300 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| NASOPHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 11 / 123 (8.94%) | 14 / 126 (11.11%) | 5 / 300 (1.67%) |
| occurrences (all) | 16 | 17 | 5 |
| OTITIS MEDIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 123 (0.00%) | 0 / 126 (0.00%) | 2 / 300 (0.67%) |
| occurrences (all) | 0 | 0 | 2 |
| OTITIS MEDIA ACUTE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 16 / 123 (13.01%) | 12 / 126 (9.52%) | 0 / 300 (0.00%) |
| occurrences (all) | 20 | 15 | 0 |
| PHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 10 / 123 (8.13%) | 6 / 126 (4.76%) | 4 / 300 (1.33%) |
| occurrences (all) | 10 | 6 | 4 |
| RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|-------------------|-------------------|-----------------|
| subjects affected / exposed | 3 / 123 (2.44%) | 3 / 126 (2.38%) | 0 / 300 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| TONSILLITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 12 / 123 (9.76%) | 6 / 126 (4.76%) | 2 / 300 (0.67%) |
| occurrences (all) | 12 | 6 | 2 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 60 / 123 (48.78%) | 59 / 126 (46.83%) | 6 / 300 (2.00%) |
| occurrences (all) | 110 | 87 | 6 |
| VIRAL INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 10 / 123 (8.13%) | 11 / 126 (8.73%) | 4 / 300 (1.33%) |
| occurrences (all) | 11 | 11 | 6 |

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | B_02_2_5 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 100 / 104 (96.15%) | | |
| Nervous system disorders | | | |
| HEADACHE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 7 / 104 (6.73%) | | |
| occurrences (all) | 8 | | |
| SOMNOLENCE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 39 / 104 (37.50%) | | |
| occurrences (all) | 51 | | |
| General disorders and administration site conditions | | | |
| CHILLS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| CRYING | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| INDURATION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 7 / 104 (6.73%) | | |
| occurrences (all) | 8 | | |
| INJECTION SITE ERYTHEMA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 59 / 104 (56.73%) | | |
| occurrences (all) | 94 | | |
| INJECTION SITE INDURATION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 41 / 104 (39.42%) | | |
| occurrences (all) | 63 | | |
| INJECTION SITE PAIN | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 99 / 104 (95.19%) | | |
| occurrences (all) | 183 | | |
| INJECTION SITE SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 50 / 104 (48.08%) | | |
| occurrences (all) | 73 | | |
| MALAISE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| PYREXIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 22 / 104 (21.15%) | | |
| occurrences (all) | 27 | | |
| SWELLING | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 6 / 104 (5.77%) | | |
| occurrences (all) | 6 | | |

| | | | |
|---|--|--|--|
| Gastrointestinal disorders DIARRHOEA alternative assessment type: Systematic subjects affected / exposed occurrences (all) NAUSEA alternative assessment type: Systematic subjects affected / exposed occurrences (all) VOMITING alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 12 / 104 (11.54%) 15 0 / 104 (0.00%) 0 8 / 104 (7.69%) 12 | | |
| Respiratory, thoracic and mediastinal disorders BRONCHOSPASM alternative assessment type: Systematic subjects affected / exposed occurrences (all) CATARRH alternative assessment type: Systematic subjects affected / exposed occurrences (all) COUGH alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 3 / 104 (2.88%) 3 | | |
| Skin and subcutaneous tissue disorders ERYTHEMA alternative assessment type: Systematic subjects affected / exposed occurrences (all) RASH alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 6 / 104 (5.77%) 6 9 / 104 (8.65%) 9 | | |

| | | | |
|---|-------------------------|--|--|
| Psychiatric disorders EATING DISORDER alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 35 / 104 (33.65%) 50 | | |
| IRRITABILITY alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 49 / 104 (47.12%) 75 | | |
| Musculoskeletal and connective tissue disorders ARTHRALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 35 / 104 (33.65%) 47 | | |
| MYALGIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| Infections and infestations BRONCHIOLITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| BRONCHITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 6 / 104 (5.77%) 6 | | |
| BRONCHOPNEUMONIA alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |
| CONJUNCTIVITIS alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 0 / 104 (0.00%) 0 | | |

| | | | |
|--|-----------------|--|--|
| EAR INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 104 (2.88%) | | |
| occurrences (all) | 3 | | |
| GASTROENTERITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| INFLUENZA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| LARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| NASOPHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 104 (4.81%) | | |
| occurrences (all) | 6 | | |
| OTITIS MEDIA | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| OTITIS MEDIA ACUTE | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 2 | | |
| PHARYNGITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 2 / 104 (1.92%) | | |
| occurrences (all) | 2 | | |
| RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 104 (0.00%) | | |
| occurrences (all) | 0 | | |
| TONSILLITIS | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 1 / 104 (0.96%) | | |
| occurrences (all) | 1 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 3 / 104 (2.88%) | | |
| occurrences (all) | 4 | | |
| VIRAL INFECTION | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 104 (3.85%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 02 May 2011 | Alignment of the protocol with the actual SAE notification and reporting process |
| 20 February 2012 | New arms to test concomitant MenB + MenC administration |
| 29 August 2013 | hSBA cut-off adjustment following serological test outsource |
| 26 November 2013 | Inclusion of an interim analysis on a subset of subjects in Group II - End of trial definition |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported