



Clinical trial results:

A phase IIIA, randomized, observer-blind, controlled, multinational study to evaluate the immunogenicity and safety of GSK Biologicals' MMR vaccine (209762) (Priorix®) at an end of shelf-life potency compared to Merck & Co., Inc.'s MMR vaccine (M M R®II), when both are co-administered with Varivax, Havrix and Prevna 13 (subset of children), and given on a two-dose schedule to healthy children in their second year of life

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-004905-26 |
| Trial protocol | FI CZ ES |
| Global end of trial date | 18 August 2015 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 15 January 2017 |
| First version publication date | 15 January 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 115649 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01681992 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, B-1330 |
| Public contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 September 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 February 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 August 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate non-inferiority of Inv_MMR vaccine compared to pooled Com_MMR vaccine lots in terms of seroresponse rates to MMR viruses at Day 42.
- To demonstrate non-inferiority of Inv_MMR vaccine compared to pooled Com_MMR vaccine lots in terms of geometric mean concentrations (GMCs) for antibodies to MMR viruses at Day 42.
- To demonstrate an acceptable immune response of Inv_MMR vaccine in terms of seroresponse rates for MMR viruses at Day 42.
- To demonstrate non-inferiority of the Inv_MMR vaccine compared to pooled Com_MMR vaccine lots in terms of seroresponse rates for mumps virus (by Plaque Reduction Neutralization Test (PRNT)) at Day 42.
- To demonstrate non-inferiority of the Inv_MMR vaccine compared to pooled Com_MMR vaccine lots in terms of geometric mean titer (GMT) for antibodies to mumps virus (by PRNT) at Day 42.

Protection of trial subjects:

All subjects were observed closely for at least 30 minutes following the administration of vaccines with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 10 October 2012 |
| 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 | Czech Republic: 700 |
| Country: Number of subjects enrolled | Finland: 421 |
| Country: Number of subjects enrolled | Malaysia: 134 |
| Country: Number of subjects enrolled | Spain: 1300 |
| Country: Number of subjects enrolled | Thailand: 966 |
| Country: Number of subjects enrolled | United States: 918 |
| Country: Number of subjects enrolled | Puerto Rico: 99 |
| Worldwide total number of subjects | 4538 |
| EEA total number of subjects | 2421 |

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) | 4538 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study had two sub-cohorts:

- US sub-cohort: Subjects recruited in the US and received the INV_MMR or COM_MMR co-administered with Varivax, Havrix and Prevnar 13 vaccines at Visit 1 (Day 0).
- Non-US sub-cohort: Subjects recruited outside the US received the INV_MMR or COM_MMR co-administered with Varivax and Havrix vaccines at Visit 1(Day 0).

Pre-assignment

Screening details:

4538 subjects were enrolled in the study, but 3 subjects were excluded because of invalid Informed Consent Forms and 19 subjects received a subject number but were not vaccinated.

Pre-assignment period milestones

| | |
|------------------------------|------|
| Number of subjects started | 4538 |
| Number of subjects completed | 4516 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Invalid Informed Consent Forms: 3 |
| Reason: Number of subjects | Subject number allocated but not vaccinated: 19 |

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind ^[1] |
| Roles blinded | Subject, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

The study was conducted in a double-blind fashion with regard to the two Inv_MMR vaccine lots (Inv_MMR_Min and Inv_MMR_Med) and in an observer-blind fashion for the lots of Inv_MMR vaccine versus the pooled Com_MMR vaccine lots. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint were all unaware of which vaccine was administered.

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Inv_MMR_ Min Group |

Arm description:

Subjects received one dose of Priorix® vaccine from a minimum potency lot (Inv_MMR_ Min) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Priorix |
| Investigational medicinal product code | 209762 |
| Other name | INV_MMR |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Two doses administered subcutaneously in the upper left arm at Day 0 and Day 42 (separate lots: Inv_MMR_Min and Inv_MMR_Med)

| | |
|---|---|
| Investigational medicinal product name | Varivax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| One dose in the upper right arm co-administered subcutaneously at Day 0 along with the study vaccines | |
| Investigational medicinal product name | Havrix 720 Junior |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose in the right thigh co-administered intramuscularly at Day 0 with the study vaccines | |
| Investigational medicinal product name | Prevnar 13 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose in the left thigh co-administered intramuscularly at Day 0 with the study vaccines | |
| Arm title | Inv_MMR_Med Group |
| Arm description: | |
| Subjects received one dose of Priorix® vaccine mid-range or medium potency lot (Inv_MMR_Med) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevna 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose. | |
| Arm type | Experimental |
| Investigational medicinal product name | Priorix |
| Investigational medicinal product code | 209762 |
| Other name | INV_MMR |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| Two doses administered subcutaneously in the upper left arm at Day 0 and Day 42 (separate lots: Inv_MMR_Min and Inv_MMR_Med) | |
| Investigational medicinal product name | Varivax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| One dose in the upper right arm co-administered subcutaneously at Day 0 along with the study vaccines | |
| Investigational medicinal product name | Havrix 720 Junior |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose in the right thigh co-administered intramuscularly at Day 0 with the study vaccines | |

| | |
|---|--------------------------|
| Investigational medicinal product name | Pevnar 13 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| One dose in the left thigh co-administered intramuscularly at Day 0 with the study vaccines | |
| Arm title | Com_MMR Group |

Arm description:

Subjects received one dose of M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Pevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) for the second dose.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Varivax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for solution for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

One dose in the upper right arm co-administered subcutaneously at Day 0 along with the study vaccines

| | |
|--|--------------------------|
| Investigational medicinal product name | Havrix 720 Junior |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose in the right thigh co-administered intramuscularly at Day 0 with the study vaccines

| | |
|--|---|
| Investigational medicinal product name | M-M-RVAXPRO |
| Investigational medicinal product code | |
| Other name | COM_MMR |
| Pharmaceutical forms | Powder and solvent for suspension for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Two doses administered subcutaneously in the upper left arm at Day 0 and Day 42

| | |
|--|--------------------------|
| Investigational medicinal product name | Pevnar 13 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

One dose in the left thigh co-administered intramuscularly at Day 0 with the study vaccines

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This is an observer blind study, wherein all study roles except the investigator are blinded.

| Number of subjects in period 1^[2] | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group |
|---|--------------------|-------------------|---------------|
| Started | 1493 | 1497 | 1526 |
| Completed | 1427 | 1427 | 1443 |
| Not completed | 66 | 70 | 83 |
| Consent withdrawn by subject | 27 | 30 | 25 |
| Adverse event, non-fatal | 3 | 2 | 3 |
| As Per Sponsor Decision | - | - | 1 |
| Lost to follow-up | 36 | 38 | 53 |
| Protocol deviation | - | - | 1 |

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 4538 subjects were enrolled in the study, but 3 subjects were excluded because of invalid Informed Consent Forms and 19 subjects received a subject number but were not vaccinated.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Inv_MMR_ Min Group |
|-----------------------|--------------------|

Reporting group description:

Subjects received one dose of Priorix® vaccine from a minimum potency lot (Inv_MMR_ Min) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose.

| | |
|-----------------------|-------------------|
| Reporting group title | Inv_MMR_Med Group |
|-----------------------|-------------------|

Reporting group description:

Subjects received one dose of Priorix® vaccine mid-range or medium potency lot (Inv_MMR_Med) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose.

| | |
|-----------------------|---------------|
| Reporting group title | Com_MMR Group |
|-----------------------|---------------|

Reporting group description:

Subjects received one dose of M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) for the second dose.

| Reporting group values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group |
|------------------------|--------------------|-------------------|---------------|
| Number of subjects | 1493 | 1497 | 1526 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|-------|-------|-------|
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 12.6 | 12.6 | 12.6 |
| standard deviation | ± 0.9 | ± 0.9 | ± 0.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 704 | 718 | 758 |
| Male | 789 | 779 | 768 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African Heritage / African American | 45 | 53 | 46 |
| American Indian or Alaskan Native | 2 | 1 | 1 |
| Asian - Central/South Asian Heritage | 1 | 0 | 2 |
| Asian - East Asian Heritage | 3 | 0 | 1 |
| Asian - South East Asian Heritage | 362 | 366 | 367 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 0 |
| White - Arabic / North African Heritage | 8 | 8 | 8 |
| White - Caucasian / European Heritage | 1017 | 1022 | 1052 |
| Other | 55 | 46 | 49 |

| | | | |
|------------------------|-------|--|--|
| Reporting group values | Total | | |
|------------------------|-------|--|--|

| | | | |
|---|------|--|--|
| Number of subjects | 4516 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2180 | | |
| Male | 2336 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African Heritage / African American | 144 | | |
| American Indian or Alaskan Native | 4 | | |
| Asian - Central/South Asian Heritage | 3 | | |
| Asian - East Asian Heritage | 4 | | |
| Asian - South East Asian Heritage | 1095 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| White - Arabic / North African Heritage | 24 | | |
| White - Caucasian / European Heritage | 3091 | | |
| Other | 150 | | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Inv_MMR_Min Group |
| Reporting group description: Subjects received one dose of Priorix® vaccine from a minimum potency lot (Inv_MMR_Min) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose. | |
| Reporting group title | Inv_MMR_Med Group |
| Reporting group description: Subjects received one dose of Priorix® vaccine mid-range or medium potency lot (Inv_MMR_Med) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose. | |
| Reporting group title | Com_MMR Group |
| Reporting group description: Subjects received one dose of M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) for the second dose. | |

Primary: Percentage of subjects with anti-measles virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA])

| | |
|--|--|
| End point title | Percentage of subjects with anti-measles virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA]) |
| End point description: For measles virus, a seroresponse was defined as post-vaccination anti-measles virus antibody concentration equal or above 200 mIU/mL (ELISA) among children who were seronegative (antibody concentration <150 mIU/mL) before dose 1. One of the study objective was to demonstrate an acceptable immune response of Inv_MMR_Min vaccine in terms of seroresponse rates for measles, mumps and rubella viruses at Day 42. Criteria: The lower limit of the two-sided 97.5% CI for the seroresponse rate of Inv_MMR_Min was to be ≥90% for antibodies to measles, mumps and rubella viruses. The same criteria was defined for demonstrating an acceptable immune response of Inv_MMR_Med vaccine. | |
| End point type | Primary |
| End point timeframe: At Day 42 | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|------------------------------------|---------------------|---------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1361 | 1366 | 1378 | |
| Units: Percentage of subjctets | | | | |
| number (confidence interval 97.5%) | 90.8 (88.9 to 92.5) | 94.2 (92.6 to 95.5) | 96.3 (95 to 97.3) | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|-----------------------------------|
| Statistical analysis description: Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42. | |
| Comparison groups | Inv_MMR_Min Group v Com_MMR Group |
| Number of subjects included in analysis | 2739 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -5.48 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -7.65 |
| upper limit | -3.43 |

Notes:

[1] - The lower limit of the two-sided 97.5% confidence interval (CI) on the group difference (Inv_MMR_Min minus Com_MMR) in seroresponse rate was to be equal or above -5% for antibodies to measles, mumps (ELISA) and rubella viruses.

| Statistical analysis title | Statistical analysis 2 |
|--|-----------------------------------|
| Statistical analysis description: Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42. | |
| Comparison groups | Inv_MMR_Med Group v Com_MMR Group |
| Number of subjects included in analysis | 2744 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[2] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -2.08 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -3.96 |
| upper limit | -0.27 |

Notes:

[2] - The lower limit of the two-sided 97.5% confidence interval for the difference in seroresponse (Inv_MMR_Med minus Com_MMR) was to be equal or above -5% for antibodies to measles, mumps (ELISA), and rubella viruses.

Primary: Percentage of subjects with anti-mumps virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA])

| | |
|--|--|
| End point title | Percentage of subjects with anti-mumps virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA]) |
| End point description: For mumps virus, a seroresponse was defined as post-vaccination anti-mumps virus antibody concentration equal or above 10 EU/mL (ELISA) among children who were seronegative (antibody concentration <5 EU/mL) before Dose 1. One of the study objective was to demonstrate an acceptable immune response of Inv_MMR_Min vaccine in terms of seroresponse rates for measles, mumps and rubella viruses at Day 42. Criteria: The lower limit of the two-sided 97.5% CI for the seroresponse rate of Inv_MMR_Min was to be $\geq 90\%$ for antibodies to measles, mumps and rubella viruses. The same criteria was defined for demonstrating an acceptable immune response of Inv_MMR_Med vaccine. | |
| End point type | Primary |

End point timeframe:

At Day 42

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|------------------------------------|---------------------|-------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1161 | 1131 | 1155 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 97.5%) | 97.4 (96.2 to 98.3) | 97.3 (96 to 98.2) | 97.8 (96.7 to 98.7) | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|--|------------------------------------|
| Statistical analysis description: Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42. | |
| Comparison groups | Com_MMR Group v Inv_MMR_ Min Group |
| Number of subjects included in analysis | 2316 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -0.42 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -1.91 |
| upper limit | 1.04 |

Notes:

[3] - The lower limit of the two-sided 97.5% confidence interval (CI) on the group difference (Inv_MMR_Min minus Com_MMR) in seroresponse rate was to be equal or above -5% for antibodies to measles, mumps (ELISA) and rubella viruses.

| Statistical analysis title | Statistical analysis 2 |
|--|-----------------------------------|
| Statistical analysis description: Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42. | |
| Comparison groups | Com_MMR Group v Inv_MMR_Med Group |
| Number of subjects included in analysis | 2286 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[4] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -0.58 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -2.11 |
| upper limit | 0.91 |

Notes:

[4] - The lower limit of the two-sided 97.5% confidence interval for the difference in seroresponse (Inv_MMR_Med minus Com_MMR) was to be equal or above -5% for antibodies to measles, mumps (ELISA) and rubella viruses.

Primary: Number of subjects with anti-mumps virus antibody concentration (by Plaque Reduction Neutralization Test [PRNT]) equal to or above the cut-off-value

| | |
|-----------------|--|
| End point title | Number of subjects with anti-mumps virus antibody concentration (by Plaque Reduction Neutralization Test [PRNT]) equal to or above the cut-off-value |
|-----------------|--|

End point description:

For mumps virus as measured by PRNT, a seroresponse was defined as post-vaccination anti-mumps virus antibody concentration equal or above 4 End point Dilution 50% (ED50) (PRNT) among children who were seronegative (antibody concentration <2.5 ED50) before Dose 1.

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

End point timeframe:

At Day 42

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|--------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1252 | 1265 | 1287 | |
| Units: Subjects | 891 | 928 | 1037 | |

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42.

| | |
|---|-----------------------------------|
| Comparison groups | Inv_MMR_Med Group v Com_MMR Group |
| Number of subjects included in analysis | 2552 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[5] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -7.22 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -10.94 |
| upper limit | -3.49 |

Notes:

[5] - The lower limit of the two-sided 97.5% CI on the group difference (Inv_MMR_Med minus pooled Com_MMR) in seroresponse rate was to be equal or above -10% for anti-mumps antibodies when tested with PRNT.

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

Statistical analysis description:

Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42.

| | |
|---|------------------------------------|
| Comparison groups | Inv_MMR_ Min Group v Com_MMR Group |
| Number of subjects included in analysis | 2539 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[6] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -9.41 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -13.2 |
| upper limit | -5.62 |

Notes:

[6] - The lower limit of the two-sided 97.5% CI on the group difference (Inv_MMR_Min minus pooled Com_MMR) in seroresponse rate was to be equal or above -10% for anti-mumps antibodies when tested with PRNT.

Primary: Percentage of subjects with anti-rubella virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA])

| | |
|-----------------|--|
| End point title | Percentage of subjects with anti-rubella virus antibody concentration equal to or above the cut-off-value (by enzyme-linked immunosorbent assay [ELISA]) |
|-----------------|--|

End point description:

For rubella virus, a seroresponse was defined as post-vaccination anti-rubella virus antibody concentration equal or above 10 IU/mL (ELISA) among children who were seronegative (antibody concentration <4 IU/mL) before Dose 1. One of the study objective was to demonstrate an acceptable immune response of Inv_MMR_Min vaccine in terms of seroresponse rates for measles, mumps and rubella viruses at Day 42. Criteria: The lower limit of the two-sided 97.5% CI for the seroresponse rate of Inv_MMR_Min was to be ≥90% for antibodies to measles, mumps and rubella viruses. The same criteria was defined for demonstrating an acceptable immune response of Inv_MMR_Med vaccine.

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

End point timeframe:

At Day 42

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1359 | 1366 | 1376 | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 97.5%) | 96.8 (95.5 to 97.7) | 97.3 (96.1 to 98.2) | 98.5 (97.6 to 99.1) | |

Statistical analyses

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

Statistical analysis description:

Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42.

| | |
|-------------------|------------------------------------|
| Comparison groups | Com_MMR Group v Inv_MMR_ Min Group |
|-------------------|------------------------------------|

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 2735 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[7] |
| Parameter estimate | Difference in seroresponse rate |
| Point estimate | -1.71 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -3.11 |
| upper limit | -0.42 |

Notes:

[7] - The lower limit of the two-sided 97.5% confidence interval (CI) on the group difference (Inv_MMR_Min minus Com_MMR) in seroresponse rate was to be equal or above -5% for antibodies to measles, mumps (ELISA) and rubella viruses.

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of seroresponse rate to measles, mumps and rubella antibodies at Day 42.

| | |
|---|-----------------------------------|
| Comparison groups | Com_MMR Group v Inv_MMR_Med Group |
| Number of subjects included in analysis | 2742 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[8] |
| Parameter estimate | Difference in seroresponse |
| Point estimate | -1.18 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 0.05 |

Notes:

[8] - The lower limit of the two-sided 97.5% confidence interval for the difference in seroresponse (Inv_MMR_Med minus Com_MMR) was to be equal or above -5% for antibodies to measles, mumps (ELISA), and rubella viruses.

Primary: Anti-measles virus antibody concentrations (ELISA)

| | |
|------------------------|---|
| End point title | Anti-measles virus antibody concentrations (ELISA) |
| End point description: | Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL |
| End point type | Primary |
| End point timeframe: | At Day 42 |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|---------------------------|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1361 | 1366 | 1378 | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 97.5%) | 2209.9 (2041.3 to 2392.4) | 2540.9 (2368.8 to 2725.5) | 2787.7 (2619.5 to 2966.7) | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for the adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups. | |
| Comparison groups | Inv_MMR_Med Group v Com_MMR Group |
| Number of subjects included in analysis | 2744 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Adjusted GMC ratio |
| Point estimate | 0.91 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.01 |

| | |
|---|------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups. | |
| Comparison groups | Com_MMR Group v Inv_MMR_ Min Group |
| Number of subjects included in analysis | 2739 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[9] |
| Parameter estimate | Adjusted GMC Ratio |
| Point estimate | 0.79 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 0.88 |

Notes:

[9] - The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (Inv_MMR_Min over pooled Com_MMR) was to be ≥ 0.67 for antibodies to measles, mumps and rubella viruses when tested with ELISA. Adjusted GMC in the Inv_MMR_Min Group = 2221.5; Adjusted GMC in the Com_MMR Group = 2798.9.

Primary: Anti-mumps virus antibody concentrations (ELISA)

| | |
|-----------------|--|
| End point title | Anti-mumps virus antibody concentrations (ELISA) |
|-----------------|--|

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in EU/mL

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

End point timeframe:

At Day 42

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|---------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1161 | 1131 | 1155 | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 97.5%) | 58.7 (55.5 to 62.1) | 60.2 (56.8 to 63.7) | 71.6 (67.7 to 75.8) | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for the adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups.

| | |
|---|-----------------------------------|
| Comparison groups | Inv_MMR_Med Group v Com_MMR Group |
| Number of subjects included in analysis | 2286 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[10] |
| Parameter estimate | Adjusted GMC ratio |
| Point estimate | 0.84 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 0.91 |

Notes:

[10] - The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (Inv_MMR_Med over pooled Com_MMR) was to be ≥ 0.67 for antibodies to measles, mumps and rubella viruses when tested with ELISA. Adjusted GMC in the Inv_MMR_Med Group = 59.4; Adjusted GMC in the Com_MMR Group = 70.6.

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

Statistical analysis description:

Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups.

| | |
|-------------------|-----------------------------------|
| Comparison groups | Inv_MMR_Min Group v Com_MMR Group |
|-------------------|-----------------------------------|

| | |
|---|---------------------------------|
| Number of subjects included in analysis | 2316 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[11] |
| Parameter estimate | Adjusted GMC ratio |
| Point estimate | 0.82 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 0.89 |

Notes:

[11] - The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (Inv_MMR_Min over pooled Com_MMR) was to be ≥ 0.67 for antibodies to measles, mumps and rubella viruses when tested with ELISA. Adjusted GMC in the Inv_MMR_Min Group = 57.8; Adjusted GMC in the Com_MMR Group = 70.6.

Primary: Anti-mumps virus antibody concentrations (by PRNT)

| | |
|---|--|
| End point title | Anti-mumps virus antibody concentrations (by PRNT) |
| End point description: | |
| Antibody concentrations are expressed as Geometric Mean Titers (GMTs) | |
| End point type | Primary |
| End point timeframe: | |
| At Day 42 | |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|--------------------|--------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1252 | 1265 | 1287 | |
| Units: Titers | | | | |
| geometric mean (confidence interval 95%) | 9.8 (9 to 10.6) | 10.7 (9.9 to 11.5) | 16.3 (15.1 to 17.7) | |

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of Geometric Mean Titer (GMT) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean titers (GMTs) and the adjusted GMT ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups. | |
| Comparison groups | Inv_MMR_Med Group v Com_MMR Group |
| Number of subjects included in analysis | 2552 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[12] |
| Parameter estimate | Adjusted GMT Ratio |
| Point estimate | 0.65 |

| | |
|---------------------|---------------|
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.57 |
| upper limit | 0.74 |

Notes:

[12] - The lower limit of the two-sided 97.5% CI on the group ratio of GMTs (Inv_MMR_Med over pooled Com_MMR) was to be ≥ 0.67 for antibodies to mumps viruses when tested with PRNT. Adjusted GMT in the Inv_MMR_Med Group = 10.2; Adjusted GMT in the Com_MMR Group = 15.6

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

Statistical analysis description:

Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of Geometric Mean Titer (GMT) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean titers (GMTs) and the adjusted GMT ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups.

| | |
|---|------------------------------------|
| Comparison groups | Inv_MMR_ Min Group v Com_MMR Group |
| Number of subjects included in analysis | 2539 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[13] |
| Parameter estimate | Adjusted GMT ratio |
| Point estimate | 0.6 |

Confidence interval

| | |
|-------------|---------------|
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.68 |

Notes:

[13] - The lower limit of the two-sided 97.5% CI on the group ratio of GMTs (Inv_MMR_Min over pooled Com_MMR) was to be ≥ 0.67 for antibodies to, mumps viruses when tested with PRNT. Adjusted GMT in the Inv_MMR_Min Group = 9.4; Adjusted GMT in the Com_MMR Group = 15.6.

Primary: Anti-rubella virus antibody concentrations (ELISA)

| | |
|-----------------|--|
| End point title | Anti-rubella virus antibody concentrations (ELISA) |
|-----------------|--|

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in IU/mL

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

End point timeframe:

At Day 42

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|--------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1359 | 1366 | 1376 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 97.5%) | 57 (54.1 to 60) | 56.9 (54.2 to 59.8) | 64.4 (61.4 to 67.5) | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: | |
| Non-inferiority of INV_MMR_MED vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups. | |
| Comparison groups | Com_MMR Group v Inv_MMR_Med Group |
| Number of subjects included in analysis | 2742 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[14] |
| Parameter estimate | Adjusted GMC ratio |
| Point estimate | 0.88 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 0.95 |

Notes:

[14] - The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (Inv_MMR_Med over pooled Com_MMR) was to be ≥ 0.67 for antibodies to measles, mumps and rubella viruses when tested with ELISA. Adjusted GMC in the Inv_MMR_Med Group = 55.6; Adjusted GMC in the Com_MMR Group = 63.0.

| | |
|---|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: | |
| Non-inferiority of INV_MMR_MIN vaccine to COM_MMR vaccine in terms of Geometric Mean Concentration (GMCs) for anti measles, anti mumps and anti rubella antibodies at Day 42. The 97.5% CI for adjusted geometric mean concentrations (GMCs) and the adjusted GMC ratio were obtained using an ANOVA model - adjustment for Country -pooled variance with more than 2 groups. | |
| Comparison groups | Com_MMR Group v Inv_MMR_Min Group |
| Number of subjects included in analysis | 2735 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[15] |
| Parameter estimate | Adjusted GMC ratio |
| Point estimate | 0.89 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 0.95 |

Notes:

[15] - The lower limit of the two-sided 97.5% CI on the group ratio of GMCs (Inv_MMR_Min over pooled Com_MMR) was to be ≥ 0.67 for antibodies to measles, mumps and rubella viruses when tested with ELISA. Adjusted GMC in the Inv_MMR_Min Group = 55.9; Adjusted GMC in the Com_MMR Group = 63.0.

Secondary: Number of subjects with anti-measles virus antibody concentration equal to or above the cut-off-value (ELISA)

| | |
|--|---|
| End point title | Number of subjects with anti-measles virus antibody concentration equal to or above the cut-off-value (ELISA) |
| End point description: | |
| For measles virus, a seroresponse was defined as post-vaccination anti-measles virus antibody concentration equal or above 200 mIU/mL (ELISA) among children who were seronegative (antibody concentration <150 mIU/mL) before Dose 1. | |
| End point type | Secondary |
| End point timeframe: | |
| At Day 84 | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 245 | 258 | 257 | |
| Units: Subjects | 244 | 254 | 253 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-mumps virus antibody concentration equal to or above the cut-off-value (ELISA)

| | |
|-----------------|---|
| End point title | Number of subjects with anti-mumps virus antibody concentration equal to or above the cut-off-value (ELISA) |
|-----------------|---|

End point description:

For mumps virus, a seroresponse was defined as post-vaccination anti-mumps virus antibody concentration equal or above 10 EU/mL (ELISA) among children who were seronegative (antibody concentration <5 EU/mL) before Dose 1.

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

End point timeframe:

At Day 84

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 216 | 199 | 212 | |
| Units: Subjects | 214 | 199 | 209 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-rubella virus antibody concentration equal to or above the cut-off-value (ELISA)

| | |
|-----------------|---|
| End point title | Number of subjects with anti-rubella virus antibody concentration equal to or above the cut-off-value (ELISA) |
|-----------------|---|

End point description:

For rubella virus, a seroresponse was defined as post-vaccination anti-rubella virus antibody concentration equal or above 10 IU/mL (ELISA) among children who were seronegative (antibody concentration <4 IU/mL) before Dose 1.

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

End point timeframe:

At Day 84

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|--------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 245 | 259 | 255 | |
| Units: Subjects | 244 | 258 | 254 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-measles virus antibody concentrations (ELISA)

| | |
|------------------------|---|
| End point title | Anti-measles virus antibody concentrations (ELISA) |
| End point description: | Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL |
| End point type | Secondary |
| End point timeframe: | |
| At Day 84 | |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|-------------------------|---------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 245 | 258 | 257 | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 95%) | 4803.5 (4290.4 to 5378) | 4557.7 (4061.5 to 5114.4) | 4453.9 (3951.9 to 5019.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-mumps virus antibody concentrations (ELISA)

| | |
|------------------------|--|
| End point title | Anti-mumps virus antibody concentrations (ELISA) |
| End point description: | Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in EU/mL |
| End point type | Secondary |
| End point timeframe: | |
| At Day 84 | |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|---------------------|----------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 216 | 199 | 212 | |
| Units: EU/mL | | | | |
| geometric mean (confidence interval 95%) | 88.9 (80.4 to 98.3) | 94.1 (85.3 to 103.8) | 86.4 (77.4 to 96.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-rubella virus antibody concentrations (ELISA)

| | |
|------------------------|--|
| End point title | Anti-rubella virus antibody concentrations (ELISA) |
| End point description: | Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in IU/mL |
| End point type | Secondary |
| End point timeframe: | At Day 84 |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|--|----------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 245 | 259 | 255 | |
| Units: IU/mL | | | | |
| geometric mean (confidence interval 95%) | 112.7 (104.1 to 122) | 110.7 (102.9 to 119.1) | 110.9 (101.8 to 120.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms (Post dose-1)

| | |
|------------------------|---|
| End point title | Number of subjects with solicited local symptoms (Post dose-1) |
| End point description: | Assessed solicited local symptoms were pain, redness and swelling. Any = Occurrence of any local symptom regardless of their intensity grade. Grade 3 Pain = Cried when limb was moved/spontaneously painful. Prevented normal every day activities. Grade 3 redness = redness with surface diameter greater than (>) 20mm. Grade 3 swelling= Grade 3 swelling = swelling with surface diameter > 20mm. |
| End point type | Secondary |
| End point timeframe: | During the 4-day (Days 0-3) post-vaccination period |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1453 | 1464 | 1482 | |
| Units: Subjects | | | | |
| Any pain | 261 | 262 | 301 | |
| Grade 3 pain | 5 | 1 | 5 | |
| Any redness | 232 | 256 | 286 | |
| Grade 3 redness | 2 | 3 | 17 | |
| Any swelling | 89 | 97 | 122 | |
| Grade 3 swelling | 2 | 3 | 6 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms (Post dose-2)

| | |
|-----------------|--|
| End point title | Number of subjects with solicited local symptoms (Post dose-2) |
|-----------------|--|

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = Occurrence of any local symptom regardless of their intensity grade. Grade 3 Pain = Cried when limb was moved/spontaneously painful. Prevented normal every day activities. Grade 3 redness = redness with surface diameter > 20mm. Grade 3 swelling= Grade 3 swelling = swelling with surface diameter > 20mm.

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

End point timeframe:

During the 4-day (Days 0-3) post-vaccination period

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1427 | 1440 | 1456 | |
| Units: Subjects | | | | |
| Any pain | 170 | 183 | 196 | |
| Grade 3 pain | 3 | 4 | 3 | |
| Any redness | 159 | 196 | 217 | |
| Grade 3 redness | 2 | 3 | 13 | |
| Any swelling | 67 | 91 | 96 | |
| Grade 3 swelling | 1 | 0 | 7 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms following the first dose.

| | |
|-----------------|--|
| End point title | Number of subjects with solicited general symptoms following the first dose. |
|-----------------|--|

End point description:

Assessed solicited general symptoms were Drowsiness, Irritability/fussiness, and loss of appetite. Any= occurrence of any general symptom regardless of intensity grade or relationship to vaccination, Grade 3 drowsiness = symptom that prevented normal activity, Grade 3 irritability/fussiness =crying that could not be comforted/ symptom that prevented normal activity, Grade 3 loss of appetite = did not eat at all.

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

End point timeframe:

During the 15-day (Days 0-14) post-vaccination period

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|----------------------------------|--------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1454 | 1466 | 1486 | |
| Units: Subjects | | | | |
| Any drowsiness | 551 | 565 | 582 | |
| Grade 3 drowsiness | 26 | 25 | 24 | |
| Any irritability / fussiness | 749 | 792 | 788 | |
| Grade 3 irritability / fussiness | 40 | 52 | 51 | |
| Any loss of appetite | 570 | 589 | 591 | |
| Grade 3 loss of appetite | 31 | 20 | 31 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting fever (Post dose-1)

| | |
|-----------------|--|
| End point title | Number of subjects reporting fever (Post dose-1) |
|-----------------|--|

End point description:

Fever was assessed for temperature $\geq 38^{\circ}\text{C}$ (any), $> 39.5^{\circ}\text{C}$ (grade 3) and related. Related = event assessed by the investigator as causally related to the study vaccination.

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

End point timeframe:

During the 43 days (Days 0-42) post-vaccination period

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1454 | 1466 | 1486 | |
| Units: Subjects | | | | |
| ≥38 °C | 582 | 617 | 618 | |
| >39.5 °C | 49 | 63 | 61 | |
| ≥38 °C related | 242 | 231 | 267 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting fever (Post dose-2)

| | |
|---|--|
| End point title | Number of subjects reporting fever (Post dose-2) |
| End point description: Fever was assessed for temperature ≥ 38°C (any), > 39.5°C (grade 3) and related. Related = event assessed by the investigator as causally related to the study vaccination. | |
| End point type | Secondary |
| End point timeframe: During the 43 days (Days 0-42) post-vaccination period. | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1426 | 1443 | 1455 | |
| Units: Subjects | | | | |
| ≥38 °C | 458 | 471 | 499 | |
| >39.5 °C | 40 | 50 | 46 | |
| ≥38 °C Related | 118 | 130 | 135 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting MMR specific solicited general symptoms (Post dose-1)

| | |
|---|--|
| End point title | Number of subjects reporting MMR specific solicited general symptoms (Post dose-1) |
| End point description: Assessed MMR specific symptoms were parotid gland swelling and any suspected signs of meningism including febrile convulsions. Any = occurrence of any general symptom regardless of intensity grade or relationship to vaccination, Grade 3 Febrile convulsion = Prevented normal, everyday activity, Grade 3 Parotid gland = Swelling with accompanied general symptoms, Related = event assessed by the investigator as causally related to the study vaccination. | |
| End point type | Secondary |

End point timeframe:

During the 43-day (Days 0-42) post-vaccination period

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1454 | 1466 | 1486 | |
| Units: Subjects | | | | |
| Any febrile convulsion | 3 | 4 | 3 | |
| Grade 3 febrile convulsion | 1 | 3 | 1 | |
| Related febrile convulsion | 1 | 0 | 2 | |
| Any parotid gland | 3 | 2 | 3 | |
| Grade 3 parotid gland | 0 | 0 | 0 | |
| Related parotid gland | 2 | 1 | 3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting MMR specific solicited general symptoms (Post dose-2)

| | |
|-----------------|--|
| End point title | Number of subjects reporting MMR specific solicited general symptoms (Post dose-2) |
|-----------------|--|

End point description:

Assessed MMR specific symptoms were parotid gland swelling and any suspected signs of meningism including febrile convulsions. Any = occurrence of any general symptom regardless of intensity grade or relationship to vaccination, Grade 3 Febrile convulsion = Prevented normal, everyday activity, Grade 3 Parotid gland = Swelling with accompanied general symptoms, Related = event assessed by the investigator as causally related to the study vaccination.

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

End point timeframe:

During the 43-day (Days 0-42) post-vaccination period

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1426 | 1443 | 1455 | |
| Units: Subjects | | | | |
| Any febrile convulsion | 2 | 6 | 4 | |
| Grade 3 febrile convulsion | 0 | 2 | 1 | |
| Related febrile convulsion | 0 | 0 | 0 | |
| Any parotid gland | 1 | 2 | 0 | |
| Grade 3 parotid gland | 0 | 0 | 0 | |
| Related parotid gland | 1 | 2 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting rash (Post dose-1)

| | |
|---|---|
| End point title | Number of subjects reporting rash (Post dose-1) |
| End point description: | |
| Assessed any rash, Grade 3, related, localized rash, generalized rash, measles/rubella like rash, and Varicella like rash. Any = occurrence of any general symptom regardless of intensity grade or relationship to vaccination. Grade 3 Measles/rubella/varicella-like rash = Rash with more than 150 lesions. Other Grade 3 Rash = Rash that prevented normal, everyday activities. Related = Rash assessed by the investigator as causally related to study vaccination. | |
| End point type | Secondary |
| End point timeframe: | |
| During the 43 days (Days 0-42) post-vaccination period | |

| End point values | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|----------------------------------|--------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1454 | 1466 | 1486 | |
| Units: Subjects | | | | |
| Any localized or generalized | 328 | 322 | 333 | |
| Any with fever | 115 | 133 | 131 | |
| Any varicella like | 57 | 53 | 45 | |
| Any measles/rubella like | 53 | 61 | 68 | |
| Any grade 3 | 15 | 21 | 24 | |
| Any related | 94 | 102 | 95 | |
| Localized any | 222 | 201 | 215 | |
| Localized administration site | 18 | 12 | 16 | |
| Localized other site | 205 | 191 | 201 | |
| Localized with fever | 65 | 68 | 71 | |
| Localized varicella like | 38 | 38 | 28 | |
| Localized measles/rubella like | 25 | 18 | 28 | |
| Localized grade 3 | 5 | 3 | 5 | |
| Localized related | 54 | 51 | 47 | |
| Generalized any | 127 | 138 | 143 | |
| Generalized with fever | 54 | 72 | 68 | |
| Generalized varicella like | 19 | 15 | 17 | |
| Generalized measles/rubella like | 29 | 43 | 41 | |
| Generalized grade 3 | 10 | 18 | 19 | |
| Generalized related | 43 | 53 | 51 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting rash (Post dose-2)

| | |
|--|---|
| End point title | Number of subjects reporting rash (Post dose-2) |
| End point description: | |
| Assessed any rash, Grade 3, related, localized rash, generalized rash, measles/rubella like rash, and Varicella like rash. Any = occurrence of any general symptom regardless of intensity grade or relationship to vaccination. Grade 3 Measles/rubella/varicella-like rash = Rash with more than 150 lesions. Other Grade 3 Rash = Rash that prevented normal, everyday activities. Related = Rash assessed by the investigator as causally related to study vaccination | |
| End point type | Secondary |
| End point timeframe: | |
| During the 43 days (Days 0-42) post-vaccination period | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|----------------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1426 | 1443 | 1455 | |
| Units: Subjects | | | | |
| Any localized or generalized | 129 | 150 | 141 | |
| Any with fever | 52 | 63 | 53 | |
| Any varicella like | 0 | 0 | 1 | |
| Any measles/rubella like | 22 | 14 | 14 | |
| Any grade 3 | 8 | 9 | 11 | |
| Any related | 26 | 24 | 29 | |
| Localized any | 75 | 83 | 71 | |
| Localized administration site | 0 | 2 | 6 | |
| Localized other site | 75 | 81 | 65 | |
| Localized with fever | 22 | 21 | 19 | |
| Localized varicella like | 0 | 0 | 0 | |
| Localized measles/rubella like | 5 | 6 | 2 | |
| Localized grade 3 | 1 | 3 | 5 | |
| Localized related | 10 | 11 | 10 | |
| Generalized any | 59 | 70 | 74 | |
| Generalized with fever | 32 | 42 | 35 | |
| Generalized varicella like | 0 | 0 | 1 | |
| Generalized measles/rubella like | 17 | 8 | 12 | |
| Generalized grade 3 | 7 | 6 | 6 | |
| Generalized related | 16 | 13 | 19 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting adverse events (Post dose-1)

| | |
|-----------------|---|
| End point title | Number of subjects reporting adverse events (Post dose-1) |
|-----------------|---|

End point description:

Any untoward medical occurrence in a patient or clinical investigation child, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

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

End point timeframe:

During the 43-day (Days 0-42) post-vaccination period

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1493 | 1497 | 1526 | |
| Units: Subjects | 762 | 794 | 777 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting adverse events (Post dose-2)

| | |
|-----------------|---|
| End point title | Number of subjects reporting adverse events (Post dose-2) |
|-----------------|---|

End point description:

Any untoward medical occurrence in a patient or clinical investigation child, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

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

End point timeframe:

During the 43-day (Days 0-42) post-vaccination period

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1493 | 1497 | 1526 | |
| Units: Subjects | 667 | 703 | 690 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting new onset chronic diseases (NOCDs)

| | |
|---|---|
| End point title | Number of subjects reporting new onset chronic diseases (NOCDs) |
| End point description: | |
| Occurrence of new onset chronic disease | |
| End point type | Secondary |
| End point timeframe: | |
| From Day 0 through the end of the study (Day 222) | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1493 | 1497 | 1526 | |
| Units: Subjects | 35 | 39 | 33 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting adverse events prompting Emergency Room (ER) visits

| | |
|--|--|
| End point title | Number of subjects reporting adverse events prompting Emergency Room (ER) visits |
| End point description: | |
| Occurrence of AEs prompting emergency room visits. | |
| End point type | Secondary |
| End point timeframe: | |
| From Day 0 through the end of the study (Day 222) | |

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1493 | 1497 | 1526 | |
| Units: Subjects | 348 | 361 | 347 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

| | |
|-----------------|--|
| End point title | Number of subjects reporting serious adverse events (SAEs) |
|-----------------|--|

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization or results in disability/incapacity.

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

End point timeframe:

From Day 0 through the end of the study (Day 222)

| End point values | Inv_MMR_Min Group | Inv_MMR_Med Group | Com_MMR Group | |
|-----------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 1493 | 1497 | 1526 | |
| Units: Subjects | 91 | 102 | 92 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

SAEs: From Day 0 to Day 222

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Inv_MMR_ Min Group |
|-----------------------|--------------------|

Reporting group description:

Subjects received one dose of Priorix® vaccine from a minimum potency lot (Inv_MMR_ Min) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose.

| | |
|-----------------------|-------------------|
| Reporting group title | Inv_MMR_Med Group |
|-----------------------|-------------------|

Reporting group description:

Subjects received one dose of Priorix® vaccine mid-range or medium potency lot (Inv_MMR_Med) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered a separate lot of the Priorix® vaccine (Inv_MMR_Release) for the second dose.

| | |
|-----------------------|---------------|
| Reporting group title | Com_MMR Group |
|-----------------------|---------------|

Reporting group description:

Subjects received one dose of M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) co-administered with Varivax® and Havrix® vaccines at Day 0. All US subjects were also co-administered Prevnar 13® vaccine. Approximately 6 weeks later at Day 42, subjects were administered M-M-R®II vaccine (Com_MMR_Lot 1 or Com_MMR_Lot 2) for the second dose.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The frequent adverse event data is currently being re-analyzed and the record will be updated once it becomes available.

| Serious adverse events | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 91 / 1493 (6.10%) | 102 / 1497 (6.81%) | 92 / 1526 (6.03%) |
| number of deaths (all causes) | 1 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |

| | | | |
|--|------------------|------------------|------------------|
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Drowning | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 4 / 1497 (0.27%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Allergy to arthropod bite | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Asthma | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental poisoning | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burns second degree | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest injury | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Child maltreatment syndrome | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Contusion | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Face injury | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Head injury | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth injury | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Poisoning | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 3 / 1526 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Nervous system disorders | | | |
| Burning sensation | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Febrile convulsion | | | |
| subjects affected / exposed | 7 / 1493 (0.47%) | 13 / 1497 (0.87%) | 8 / 1526 (0.52%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 15 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Hypochromic anaemia | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 3 / 1497 (0.20%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 | | | |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Constipation | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 / 1493 (0.00%) | 3 / 1497 (0.20%) | 4 / 1526 (0.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Food poisoning | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 3 / 1493 (0.20%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Perianal erythema | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Teething | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|------------------|------------------|------------------|
| Angioedema | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Henoch-schonlein purpura | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Rash | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stevens-johnson syndrome | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| 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 | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 6 / 1493 (0.40%) | 7 / 1497 (0.47%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 1493 (0.27%) | 10 / 1497 (0.67%) | 8 / 1526 (0.52%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 10 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis viral | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 2 / 1497 (0.13%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis orbital | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 3 / 1497 (0.20%) | 4 / 1526 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis klebsiella | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 3 / 1526 (0.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Empyema | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis brain stem | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Exanthema subitum | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 16 / 1493 (1.07%) | 19 / 1497 (1.27%) | 10 / 1526 (0.66%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 19 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 rotavirus | | | |
| subjects affected / exposed | 6 / 1493 (0.40%) | 3 / 1497 (0.20%) | 7 / 1526 (0.46%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 2 / 1497 (0.13%) | 4 / 1526 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpangina | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 1 / 1497 (0.07%) | 3 / 1526 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 1493 (0.20%) | 2 / 1497 (0.13%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 1 / 1497 (0.07%) | 4 / 1526 (0.26%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngotracheitis obstructive | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Meningitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Nail bed infection | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 | 2 / 1493 (0.13%) | 3 / 1497 (0.20%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nosocomial infection | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |

| | | | |
|---|------------------|-------------------|-------------------|
| subjects affected / exposed | 3 / 1493 (0.20%) | 3 / 1497 (0.20%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media viral | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Otosalpingitis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 1493 (0.20%) | 2 / 1497 (0.13%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 5 / 1497 (0.33%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 1493 (0.47%) | 14 / 1497 (0.94%) | 10 / 1526 (0.66%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 14 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 2 / 1497 (0.13%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 3 / 1493 (0.20%) | 1 / 1497 (0.07%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 6 / 1497 (0.40%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| 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 bronchitis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 2 / 1497 (0.13%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhinitis | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 1 / 1497 (0.07%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin candida | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 1 / 1497 (0.07%) | 0 / 1526 (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 |
| Tonsillitis | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 1493 (0.13%) | 3 / 1497 (0.20%) | 3 / 1526 (0.20%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 1493 (0.13%) | 1 / 1497 (0.07%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 3 / 1493 (0.20%) | 1 / 1497 (0.07%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral tonsillitis | | | |
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 1493 (0.27%) | 7 / 1497 (0.47%) | 6 / 1526 (0.39%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 7 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 1493 (0.07%) | 0 / 1497 (0.00%) | 0 / 1526 (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 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 2 / 1526 (0.13%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 1 / 1526 (0.07%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Inv_MMR_ Min Group | Inv_MMR_Med Group | Com_MMR Group |
|---|--------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 1493 (0.00%) | 0 / 1497 (0.00%) | 0 / 1526 (0.00%) |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 17 February 2014 | <ul style="list-style-type: none">At CBER's request, the US non post dose 2 subcohort was eliminated. This subcohort was previously defined as any child enrolled in the US after the target enrollment of 1000 US children was met. These children would not have been required to have a blood sample taken post dose 2 as post dose 2 immunogenicity testing was only required in 1000 children. At CBER's request, the serologic response after each dose of both Merck's MMR-II and GSK's investigational vaccine will be evaluated in all US children. In the event that the pre-specified criteria for seroresponse are not met, U.S. children will be offered vaccination with MMR-II to assure protection from measles, mumps and rubella diseases.Vaccination against influenza and haemophilus influenza type B can be given at any time before, during, or after the study, including the day of study vaccination. This is to correct a prior exclusion criterion which stated that it could be given at any time during the study. The intent has always been to allow these vaccinations at any time regardless of whether or not it was before, during or after the study period.For other MMR US Phase III studies, CBER has requested that all conditions leading to non-routine medically attended visits be collected for the entire study in the eCRF. It has been clarified throughout the protocol that From Visit 1 (Day 0) to study end (Day 222), all medically attended events will be recorded in the eCRF. Subjects' routine 'well child' doctor visits will not be recorded in the eCRF. |
| 19 May 2015 | <ul style="list-style-type: none">Serological assays for the determination of antibodies against measles, rubella and varicella viruses will now be performed by a new 3rd party Contract Research Organization (CRO) named NEOMED-LABS Inc. Initially the testing was planned to be performed by GSK Biologicals' laboratory in Rixensart. The assays have been transferred to GSK Biologicals' laboratory in Laval. As of April 1st 2015, the GSK Biologicals' laboratory in Laval became part of Neomed. The only change between GSK Biologicals' laboratory in Laval and NEOMED-LABS Inc. is the name of the laboratory: assays and facilities remain the same.Due to a delay in the availability of serologic data for the mumps Plaque Reduction Neutralization Test (PRNT) data analysis for this study will be conducted as follows: Part 1 will include a summary of measles, mumps and rubella Enzyme-Linked Immunosorbent Assay (ELISA) results post dose 1 (Day 42) and post dose 2 (Day 84). Part 2 will include a full immunogenicity analysis for post dose 1 (Day 42) and post dose 2 (Day 84) including mumps PRNT results post dose 1, and all safety data |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported