# Clinical trial results:
# A phase IIIA, randomized, observer-blind, controlled, multinational study to evaluate the safety and immunogenicity of GSK Biologicals' MMR vaccine (209762) (Priorix®) compared to Merck & Co., Inc.'s MMR vaccine (M M R®II or VaxPro), as a first dose, both co-administered with Varivax, Havrix (all subjects) and Prevnar 13 (US subset) in healthy children 12 to 15 months of age

## Summary

| | |
|---|---|
| EudraCT number | 2011-006161-18 |
| Trial protocol | EE FI |
| Global end of trial date | 22 December 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 12 January 2017 |
| First version publication date | 12 January 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 115650 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02184572 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline Biologicals |
| Sponsor organisation address | Rue de l'Institut 89, Rixensart, Belgium, |
| Public contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com |
| Scientific contact | Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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 | 22 December 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 December 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

• To demonstrate the safety profile (fever >39.0°C (>102.2°F)) of Inv_MMR compared to Com_MMR (pooled lots) when co-administered with VV and HAV (to all children) and PCV-13 (only to children enrolled in the US).
• To demonstrate the safety profile (fever ≥38.0°C (≥100.4°F)) of Inv_MMR compared to Com_MMR (pooled lots) when co-administered with VV and HAV (to all children) and PCV-13 (children enrolled in the US).

Protection of trial subjects:

All subjects were supervised for at least 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 August 2014 |
| 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 | Estonia: 240 |
| Country: Number of subjects enrolled | Finland: 220 |
| Country: Number of subjects enrolled | Puerto Rico: 23 |
| Country: Number of subjects enrolled | Taiwan: 185 |
| Country: Number of subjects enrolled | United States: 1075 |
| Worldwide total number of subjects | 1743 |
| EEA total number of subjects | 460 |

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 | 1743 |

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

US sub-cohort: Subjects recruited in US received INV_MMR (Priorix®)or COM_MMR (M-M-R®II/M-M-R Vax Pro™) co-administered with Varivax®, Havrix® & Prevnar 13 vaccines (Day 0). Non-US sub-cohort: Subjects recruited outside the US received INV_MMR (Priorix®) or COM_MMR (M-M-R®II/M-M-R Vax Pro™) co-administered with Varivax® & Havrix® vaccines (Day 0).

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 1742[1] |
| Number of subjects completed | 1736 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Subject no. allocated vaccine not administered: 6 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 1743 subjects enrolled, 1 subject was removed from the study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Blinding implementation details:

Observer blinded study

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | INV_MMR |

Arm description:

Subjects received 1 dose of the study vaccine Priorix® co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Priorix® |
| Investigational medicinal product code | |
| Other name | GSK Biologicals' measles, mumps, and rubella vaccine live |
| Pharmaceutical forms | Powder and solvent for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1 dose administered subcutaneously (SC) in the tricep region of left arm.

| | |
|---|---|
| Investigational medicinal product name | Havrix® |
| Investigational medicinal product code | SUB38555 |
| Other name | Havrix junior 720 (GSK Biological Hepatitis A virus antigen (HAV)) |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered intramuscularly (IM) in the anterolateral region of the right thigh at Visit 1 (Day 0),

with either Inv_MMR vaccine or one of the two Com_MMR vaccine lots.

| | |
|---|---|
| Investigational medicinal product name | Varivax® |
| Investigational medicinal product code | SUB25312 |
| Other name | Merck & Co. Inc.'s Live attenuated Varicella |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered SC in the tricep region of right arm at Visit 1 (Day 0), with either Priorix® vaccine or one of the two M-M-R®II vaccine lots.

| | |
|---|---|
| Investigational medicinal product name | Prevnar 13® |
| Investigational medicinal product code | |
| Other name | Pfizer Inc.'s Pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein) (PCV-13) |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered IM in the anterolateral region of the left thigh at Visit 1 (Day 0), with either Inv_MMR vaccine or one of the two Com_MMR vaccine lots in US children only.

| | |
|---|---|
| **Arm title** | COM_MMR |

Arm description:

Subjects received 1 dose of the licensed vaccine M-M-R®II or M-M-R Vax Pro™ Lot 1 or Lot 2 co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | M-M-R®II |
| Investigational medicinal product code | |
| Other name | M-M-R Vax Pro® |
| Pharmaceutical forms | Powder and solvent for suspension for injection in pre-filled syringe |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

1 dose administered SC in the tricep region of left arm.

| | |
|---|---|
| Investigational medicinal product name | Havrix® |
| Investigational medicinal product code | SUB38555 |
| Other name | Havrix junior 720 (GSK Biological Hepatitis A virus antigen (HAV)) |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered intramuscularly (IM) in the anterolateral region of the right thigh at Visit 1 (Day 0), with either Inv_MMR vaccine or one of the two Com_MMR vaccine lots.

| | |
|---|---|
| Investigational medicinal product name | Varivax® |
| Investigational medicinal product code | SUB25312 |
| Other name | Merck & Co. Inc.'s Live attenuated Varicella |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered SC in the tricep region of right arm at Visit 1 (Day 0), with either Priorix® vaccine or one of the two M-M-R®II vaccine lots.

| | |
|---|---|
| Investigational medicinal product name | Prevnar 13® |
| Investigational medicinal product code | |
| Other name | Pfizer Inc.'s Pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein) (PCV-13) |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Intramuscular use |

Dosage and administration details:

1 dose administered IM in the anterolateral region of the left thigh at Visit 1 (Day 0), with either Inv_MMR vaccine or one of the two Com_MMR vaccine lots in US children only.

| **Number of subjects in period 1[2]** | INV_MMR | COM_MMR |
|---|---|---|
| Started | 1163 | 573 |
| Completed | 1116 | 543 |
| Not completed | 47 | 30 |
| Consent withdrawn by subject | 14 | 9 |
| Loss Of Kaiser Insurance | 1 | - |
| 2nd blooddraw & diary card incomplete | 1 | - |
| Traveling Outside The Country | 1 | - |
| Lost to follow-up | 29 | 21 |
| Family Out Of Country Until 9/29/2015 | 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: Out of 1743 subjects enrolled, 6 subjects with an allocated subject number did not receive the study vaccine dose and 1 subject was removed from the study.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | INV_MMR |
| Reporting group description: | |
| Subjects received 1 dose of the study vaccine Priorix® co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0. | |
| Reporting group title | COM_MMR |
| Reporting group description: | |
| Subjects received 1 dose of the licensed vaccine M-M-R®II or M-M-R Vax Pro™ Lot 1 or Lot 2 co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0. | |

| Reporting group values | INV_MMR | COM_MMR | Total |
|---|---|---|---|
| Number of subjects | 1163 | 573 | 1736 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: months | | | |
| arithmetic mean | 12.3 | 12.3 | |
| standard deviation | ± 0.7 | ± 0.7 | - |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 551 | 270 | 821 |
| Male | 612 | 303 | 915 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African Heritage / African American | 64 | 38 | 102 |
| American Indian or Alaskan Native | 29 | 16 | 45 |
| Asian - Central/South Asian Heritage | 8 | 5 | 13 |
| Asian - East Asian Heritage | 131 | 65 | 196 |
| Asian - Japanese Heritage | 2 | 0 | 2 |
| Asian - South East Asian Heritage | 28 | 12 | 40 |
| Native Hawaiian or Other Pacific Islander | 1 | 2 | 3 |
| White - Arabic / North African Heritage | 3 | 3 | 6 |
| White - Caucasian / European Heritage | 808 | 385 | 1193 |
| Other | 89 | 47 | 136 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | INV_MMR |
| Reporting group description: | |
| Subjects received 1 dose of the study vaccine Priorix® co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0. | |
| Reporting group title | COM_MMR |
| Reporting group description: | |
| Subjects received 1 dose of the licensed vaccine M-M-R®II or M-M-R Vax Pro™ Lot 1 or Lot 2 co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0. | |

### Primary: Number of subjects reporting fever after MMR (Priorix® or M-M-R®II ) vaccination

| | |
|---|---|
| End point title | Number of subjects reporting fever after MMR (Priorix® or M-M-R®II ) vaccination |
| End point description: | |
| Fever was assessed for temperature equal to/above (≥) 38°C and above (>) 39.0°C. The safety profile for fever was assessed based on the group difference (INV_MMR minus COM_MMR) in incidence of fever equal to or below the cut-off value. | |
| End point type | Primary |
| End point timeframe: | |
| During Day 5 to Day 12 post-vaccination period | |

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1125 | 556 | | |
| Units: Subjects | | | | |
| ≥38 °C | 205 | 95 | | |
| >39.0 °C | 47 | 17 | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical analysis 1 |
| Statistical analysis description: | |
| Null hypotheses: UL of the group difference (INV_MMR minus COM_MMR) in incidence of 95% CI is equal to or below (≤) 10% for Fever ≥38°C and equal to or below (≤) 5% for Fever >39.0°C. | |
| Comparison groups | INV_MMR v COM_MMR |

| | |
|---|---|
| Number of subjects included in analysis | 1681 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Parameter estimate | Difference in percentage between groups |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.84 |
| upper limit | 4.89 |

Notes:

[1] - Power obtained using PASS 2005 (Likelihood Score [Miettinen and Nurminen approach]), [Miettinen, 1985]), one-sided non-inferiority test for the difference of two independent proportions, under the alternative associated to the reference value & one-sided alpha=2.5%. The global power for these objectives was 90.3%

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

Statistical analysis description:

Null hypotheses: UL of the group difference (INV_MMR minus COM_MMR) in incidence of 95% CI is equal to or below (≤) 10% for Fever ≥38°C and equal to or below (≤) 5% for Fever >39.0°C.

| | |
|---|---|
| Comparison groups | INV_MMR v COM_MMR |
| Number of subjects included in analysis | 1681 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Parameter estimate | Difference in percentage between groups |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.92 |
| upper limit | 2.9 |

Notes:

[2] - Power obtained using PASS 2005 (Likelihood Score [Miettinen and Nurminen approach]), [Miettinen, 1985]), one-sided non-inferiority test for the difference of two independent proportions, under the alternative associated to the reference value & one-sided alpha=2.5%. The global power for these objectives was 90.3%.

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

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

End point description:

Seroresponse was defined as post-vaccination anti-measles virus antibody concentration ≥200 mIU/mL (ELISA, Enzygnost) among children who were seronegative (antibody concentration <150 mIU/mL) before vaccination.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1042 | 522 | | |
| Units: subjects | | | | |
| ≥150 mIU/ml | 1035 | 505 | | |
| ≥200 mIU/ml | 1032 | 504 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Evaluation of immunogenicity in terms of anti-measles virus antibody concentrations

| End point title | Evaluation of immunogenicity in terms of anti-measles virus antibody concentrations |
|---|---|

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL. Analyses included initially seronegative subjects only.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1042 | 522 | | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 95%) | 2751.2 (2617.6 to 2891.7) | 3134 (2879.6 to 3410.8) | | |

### 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

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

End point description:

For mumps virus, a seroresponse was defined as post-vaccination anti-mumps virus antibody concentration ³10 EU/mL (ELISA, PPD) among children who were seronegative (antibody concentration <5 EU/mL) before vaccination.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 963 | 484 | | |
| Units: Subjects | | | | |
| ≥5 EU/ml | 961 | 481 | | |
| ≥10 EU/ml | 957 | 474 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Evaluation of immunogenicity in terms of anti-mumps virus antibody concentrations

| End point title | Evaluation of immunogenicity in terms of anti-mumps virus antibody concentrations |
|---|---|

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL. Analyses included initially seronegative subjects only.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 963 | 484 | | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 95%) | 86 (82 to 90.3) | 82.6 (76.5 to 89.2) | | |

### 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

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

End point description:

For rubella virus, a seroresponse was defined as post-vaccination anti-rubella virus antibody concentration ³10 IU/mL (ELISA, Enzygnost) among children who were seronegative (antibody concentration <4 IU/mL) before vaccination.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1042 | 522 | | |
| Units: subjects | | | | |
| ≥10 IU/ml | 997 | 513 | | |
| ≥4 IU/ml | 1038 | 521 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Evaluation of immunogenicity in terms of anti-rubella virus antibody concentrations

| End point title | Evaluation of immunogenicity in terms of anti-rubella virus antibody concentrations |
|---|---|

End point description:

Antibody concentrations are expressed as Geometric Mean Concentrations (GMCs) in mIU/mL. Analyses included initially seronegative subjects only.

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

End point timeframe:

At Day 42 post vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1042 | 522 | | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 95%) | 45 (42.8 to 47.2) | 66.8 (62.2 to 71.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with solicited local symptoms

| End point title | Number of subjects with solicited local symptoms |
|---|---|

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.

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

End point timeframe:

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

| **End point values** | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1122 | 554 | | |
| Units: Subjects | | | | |
| Any pain | 311 | 132 | | |
| Grade 3 pain | 6 | 2 | | |
| Any redness | 259 | 138 | | |
| Grade 3 redness (>20 mm) | 7 | 8 | | |
| Any swelling | 95 | 59 | | |
| Grade 3 swelling (>20 mm) | 2 | 3 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with solicited general symptoms

| End point title | Number of subjects with solicited general symptoms |
|---|---|

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 | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1125 | 556 | | |
| Units: Subjects | | | | |
| Any drowsiness | 526 | 239 | | |
| Grade 3 drowsiness | 31 | 13 | | |
| Any irritability/fussiness | 721 | 346 | | |
| Grade 3 irritability/fussiness | 41 | 20 | | |
| Any loss of appetite | 492 | 233 | | |
| Grade 3 loss of appetite | 20 | 10 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting fever

| End point title | Number of subjects reporting fever |
|---|---|

End point description:

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

End point timeframe:

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

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1125 | 556 | | |
| Units: Subjects | | | | |
| ≥38 °C | 349 | 180 | | |
| >39.5 °C | 45 | 15 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting MMR specific solicited general symptoms

| End point title | Number of subjects reporting MMR specific solicited general symptoms |
|---|---|

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 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 | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1125 | 556 | | |
| Units: Subjects | | | | |
| Any febrile convulsion | 2 | 0 | | |
| Grade 3 febrile convulsion | 1 | 0 | | |
| Related febrile convulsion | 1 | 0 | | |
| Any parotid gland swelling | 0 | 0 | | |

| | | | | |
|---|---|---|---|---|
| Grade 3 parotid gland swelling | 0 | 0 | | |
| Related parotid gland swelling | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting investigator-confirmed rash

| End point title | Number of subjects reporting investigator-confirmed rash |
|---|---|

End point description:

Assessed any rash, Grade 3, Related, Localized rash, Generalized rash, measles/rubella-rash. Grade 3 Measles/rubella/varicella-like rash = Rash with more than150 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-day (Days 0-42) post-vaccination period

| **End point values** | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1125 | 556 | | |
| Units: Subjects | | | | |
| Any localized or generalized | 274 | 153 | | |
| Any with fever | 99 | 49 | | |
| Any varicella like | 39 | 23 | | |
| Any measles/rubella like | 65 | 26 | | |
| Any grade 3 | 22 | 8 | | |
| Any related | 70 | 37 | | |
| Localized any | 185 | 98 | | |
| Localized administration site | 8 | 4 | | |
| Localized other site | 177 | 96 | | |
| Localized with fever | 53 | 26 | | |
| Localized varicella like | 26 | 14 | | |
| Localized measles/rubella like | 22 | 12 | | |
| Localized grade 3 | 2 | 1 | | |
| Localized related | 24 | 21 | | |
| Generalized any | 108 | 65 | | |
| Generalized with fever | 48 | 25 | | |
| Generalized varicella like | 13 | 9 | | |
| Generalized measles/rubella like | 45 | 16 | | |
| Generalized grade 3 | 20 | 7 | | |
| Generalized related | 47 | 20 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting unsolicited adverse events

| End point title | Number of subjects reporting unsolicited adverse events |
|---|---|

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 | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | 597 | 278 | | |

### 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:

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

End point timeframe:

Day 0 through the end of the study (Day 180)

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | 29 | 11 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting adverse events prompting ER visits

| End point title | Number of subjects reporting adverse events prompting ER visits |
|---|---|

End point description:

Occurrence of AEs prompting emergency room (ER) visits.

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

End point timeframe:

Day 0 through the end of the study (Day 180)

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | 166 | 55 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting AEs leading to a medically attended visit

| End point title | Number of subjects reporting AEs leading to a medically attended visit |
|---|---|

End point description:

An event for which the child received medical attention defined as hospitalization, an emergency room visit or a visit to or from medical personnel (e.g., nurse practitioner or physician assistant or medical doctor) for any reason.

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

End point timeframe:

Day 0 through the end of the study (Day 180)

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | 717 | 319 | | |

### 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 resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization or resulted in

disability/incapacity.

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

End point timeframe:

Day 0 through the end of the study (Day 180)

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | 24 | 9 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting measles-like illness

| End point title | Number of subjects reporting measles-like illness |
|---|---|

End point description:

Measles-like illness was defined as the occurrence of the following signs and symptoms in the absence of another confirmed diagnosis: maculopapular rash, fever (≥38°C), and at least one symptom of cough, coryza, conjunctivitis, or diarrhea, with fever or rash occurring between Day 5 and Day 12 inclusive. Other event must be one of cough, coryza, conjunctivitis, or diarrhea.

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

End point timeframe:

Between Day 5 and Day 12 (inclusive) post-vaccination

| End point values | INV_MMR | COM_MMR | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1163 | 573 | | |
| Units: Subjects | | | | |
| Measles-like illness | 18 | 5 | | |
| Maculopapular rash plus fever and one other event | 26 | 9 | | |
| Maculopapular rash and fever | 89 | 44 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

Serious Adverse events (SAE) =Entire study period (180 days).

Adverse event reporting additional description:

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

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | INV_MMR Group |

Reporting group description:

Subjects received 1 dose of the study vaccine Priorix® co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0.

| | |
|---|---|
| Reporting group title | COM_MMR Group |

Reporting group description:

Subjects received 1 dose of the licensed vaccine M-M-R®II or M-M-R Vax Pro™ Lot 1 or Lot 2 co administered with Varivax® and Havrix® vaccines at Day 0. Subjects recruited in the US also received Prevnar 13® at Day 0.

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 Group | COM_MMR Group | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 1163 (2.06%) | 9 / 573 (1.57%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Febrile convulsion | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial hyperreactivity | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 2 / 573 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Exanthema subitum | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Otitis media | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 1163 (0.34%) | 1 / 573 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salmonellosis | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tonsillitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 1163 (0.26%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 1163 (0.09%) | 0 / 573 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | INV_MMR Group | COM_MMR Group | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 1163 (0.00%) | 0 / 573 (0.00%) | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported