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 Prevnar 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 (seperate 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 subcutaneosly 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 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 (seperate 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 subcutaneosly 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	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 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.

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 subcutaneosly 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 adminsitered subcutaneously in the upper left arm at Day 0 and Day 42

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

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 subjcets				
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 ≥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 - adjustement 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 - adjustement 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 - adjustement 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 - adjustement 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 - adjustement 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 - adjustement 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 - adjustement 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 - adjustement 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 ≥ 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	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 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 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	• 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	• 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