



Clinical trial results:

Open, randomised, controlled, multicenter Phase IIIb study to evaluate the immune response and safety, after the administration of GlaxoSmithKline Biologicals live attenuated measles mumps rubella varicella (MMRV) combination vaccine (Priorix tetra) or MMRV + conjugated meningococcal C vaccine (MenC) (Meningitec, Wyeth Vaccines) given to healthy children.

Summary

EudraCT number	2011-001608-37
Trial protocol	IT
Global end of trial date	31 March 2014

Results information

Result version number	v2
This version publication date	28 April 2016
First version publication date	31 May 2015
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Data for secondary endpoints have been added.

Trial information

Trial identification

Sponsor protocol code	115555
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01506193
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, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of MMRV vaccine co-administered with MenC conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-measles, anti-mumps, anti-rubella, and anti-varicella seroconversion rates at Day 42 after dose 1.

To demonstrate the non-inferiority of MenC conjugate vaccine coadministered with MMRV compared to MenC conjugate vaccine alone with respect to rSBA-MenC antibody seroprotection rates at Day 42 after vaccination.

Protection of trial subjects:

The subjects will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccine(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 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	Italy: 716
Worldwide total number of subjects	716
EEA total number of subjects	716

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)	716
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MMRV + MenC Group

Arm description:

Subjects who received MenC vaccine co-administered along with MMRV vaccine at Visit 1 (Day 0).

Arm type	Experimental
Investigational medicinal product name	PRIORIX TETRA*SC 1FL+1F 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One dose of MMRV vaccine administered subcutaneously in the deltoid region of the left arm

Investigational medicinal product name	MENINGITEC*INIET 1FL 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of MenC vaccine administered intramuscularly in the tricep of the right arm

Arm title	MMRV Group
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Arm description:

Subjects who received MMRV vaccine at Visit 1 (Day 0) and MenC vaccine at Visit 2 (Days 35-49).

Arm type	Active comparator
Investigational medicinal product name	PRIORIX TETRA*SC 1FL+1F 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One dose of MMRV vaccine administered subcutaneously in the deltoid region of the left arm

Investigational medicinal product name	MENINGITEC*INIET 1FL 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of MenC vaccine administered intramuscularly in the tricep of the right arm

Arm title	MenC Group
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Arm description:

Subjects who received MenC vaccine at Visit 1 (Day 0) and MMRV vaccine at Visit 2 (Days 35-49)

Arm type	Active comparator
Investigational medicinal product name	PRIORIX TETRA*SC 1FL+1F 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One dose of MMRV vaccine administered subcutaneously in the deltoid region of the left arm

Investigational medicinal product name	MENINGITEC*INIET 1FL 0,5ML
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of MenC vaccine administered intramuscularly in the tricep of the right arm

Number of subjects in period 1	MMRV + MenC Group	MMRV Group	MenC Group
Started	351	183	182
Completed	337	179	168
Not completed	14	4	14
Consent withdrawn by subject	5	1	8
Protocol violation	1	-	1
Adverse event, non-fatal	-	-	1
Migrated/moved from study area	-	-	1
Lost to follow-up	8	3	3

Baseline characteristics

Reporting groups

Reporting group title	MMRV + MenC Group
Reporting group description:	
Subjects who received MenC vaccine co-administered along with MMRV vaccine at Visit 1 (Day 0).	
Reporting group title	MMRV Group
Reporting group description:	
Subjects who received MMRV vaccine at Visit 1 (Day 0) and MenC vaccine at Visit 2 (Days 35-49).	
Reporting group title	MenC Group
Reporting group description:	
Subjects who received MenC vaccine at Visit 1 (Day 0) and MMRV vaccine at Visit 2 (Days 35-49)	

Reporting group values	MMRV + MenC Group	MMRV Group	MenC Group
Number of subjects	351	183	182
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: months			
arithmetic mean	13.4	13.4	13.4
standard deviation	± 0.6	± 0.6	± 0.7
Gender categorical			
Units: Subjects			
Female	167	85	88
Male	184	98	94

Reporting group values	Total		
Number of subjects	716		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: months arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	340		
Male	376		

End points

End points reporting groups

Reporting group title	MMRV + MenC Group
Reporting group description:	
Subjects who received MenC vaccine co-administered along with MMRV vaccine at Visit 1 (Day 0).	
Reporting group title	MMRV Group
Reporting group description:	
Subjects who received MMRV vaccine at Visit 1 (Day 0) and MenC vaccine at Visit 2 (Days 35-49).	
Reporting group title	MenC Group
Reporting group description:	
Subjects who received MenC vaccine at Visit 1 (Day 0) and MMRV vaccine at Visit 2 (Days 35-49)	

Primary: Number of seroconverted subjects for measles, mumps, rubella, and varicella virus

End point title	Number of seroconverted subjects for measles, mumps, rubella, and varicella virus ^[1]
End point description:	
Seroconversion was defined as the appearance of antibodies (i.e. concentration/titre \geq the cut-off value) in the serum of subjects seronegative before vaccination. The cut-off values for seroconversion was 150 mIU/mL, 231 U/mL, 4 IU/mL and 25 mIU/mL for measles, mumps, rubella and varicella, respectively.	
End point type	Primary
End point timeframe:	
42 days after vaccination	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome measure concerns subjects in MMRV + MenC Group and MMRV Group only. Subjects in MMRV Group did not receive MenC vaccine.

End point values	MMRV + MenC Group	MMRV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	164		
Units: Subjects				
Anti-measles \geq 150 mIU/mL [N=307, 163]	305	162		
Anti-mumps \geq 231 U/mL [N=309, 162]	292	151		
Anti-rubella \geq 4 IU/mL [N=309, 164]	309	164		
Anti-varicella \geq 25 mIU/mL [N= 300, 159]	299	159		

Statistical analyses

Statistical analysis title	Immune response for anti-measles antibodies
Statistical analysis description:	
Non-inferiority of MMRV vaccine co-administered with MenC conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-measles seroconversion rates (SCRs) at Day 42 after dose 1. Non-inferiority with respect to seroconversion rates for measles was concluded if the lower limit of the 95% CI around the difference in seroconversion rates between groups would be $[-10\%]$ or	

higher.

Comparison groups	MMRV + MenC Group v MMRV Group
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentage
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.82
upper limit	2.78

Statistical analysis title	Immune response for anti-mumps antibodies
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Statistical analysis description:

Non-inferiority of MMRV vaccine co-administered with MenC conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-mumps seroconversion rates (SCRs) at Day 42 after dose 1. Non-inferiority with respect to seroconversion rates for mumps was concluded if the lower limit of the 95% CI around the difference in seroconversion rates between groups would be [-10%] or higher.

Comparison groups	MMRV Group v MMRV + MenC Group
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentage
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	6.67

Statistical analysis title	Immune response for anti-rubella antibodies
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Statistical analysis description:

Non-inferiority of MMRV vaccine co-administered with MenC conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-rubella seroconversion rates (SCRs) at Day 42 after dose 1. Non-inferiority with respect to seroconversion rates for rubella was concluded if the lower limit of the 95% CI around the difference in seroconversion rates between groups would be [-10%] or higher.

Comparison groups	MMRV + MenC Group v MMRV Group
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentage
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	2.29

Statistical analysis title	Immune response for anti-varicella antibodies
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Statistical analysis description:

Non-inferiority of MMRV vaccine co-administered with MenC conjugate vaccine compared to the first dose of MMRV vaccine alone with respect to anti-varicella seroconversion rates (SCRs) at Day 42 after dose 1. Non-inferiority with respect to seroconversion rates for varicella was concluded if the lower limit of the 95% CI around the difference in seroconversion rates between groups would be [-10%] or higher.

Comparison groups	MMRV + MenC Group v MMRV Group
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentage
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	2.03

Primary: Number of seroprotected subjects for rSBA-MenC antibodies

End point title	Number of seroprotected subjects for rSBA-MenC antibodies ^[2]
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End point description:

Seroprotection was defined as the appearance of rSBA-MenC antibody titre $\geq 1:8$

End point type	Primary
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End point timeframe:

At 42 days after vaccination

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome measure concerns subjects in MMRV + MenC Group and MenC Group only.

End point values	MMRV + MenC Group	MenC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	143		
Units: Subjects				
rSBA-MenC $\geq 1:8$	286	142		

Statistical analyses

Statistical analysis title	Immune response for rSBA-MenC antibodies
Statistical analysis description:	
Non-inferiority of MenC conjugate vaccine co-administered with MMRV compared to MenC conjugate vaccine alone with respect to rabbit complement serum bactericidal assay (rSBA-MenC) antibody seroprotection rates (SPRs) at Day 42 after vaccination. Non-inferiority with respect to seroresponse for rSBA-MenC was concluded if the lower limit of the 95% CI around the difference in seroprotection rates between groups would be [-10%] or higher.	
Comparison groups	MMRV + MenC Group v MenC Group
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Difference in percentage
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.39
upper limit	2.24

Secondary: Number of subjects reporting any and grade 3 solicited local symptoms

End point title	Number of subjects reporting any and grade 3 solicited local symptoms ^[3]
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End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = Cried when limb is moved/spontaneously painful. Grade 3 redness/swelling = redness/swelling spreading beyond 20 millimeters (mm) of injection site. This outcome measure concerns subjects in MMRV + MenC Group and MMRV Group only. Subjects in MMRV Group did not receive MenC vaccine.

End point type	Secondary
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End point timeframe:

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

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This outcome measure concerns subjects in MMRV + MenC Group and MMRV Group only. Subjects in MMRV Group did not receive MenC vaccine.

End point values	MMRV + MenC Group	MMRV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	177		
Units: Subjects				
Any Pain, Men C	79	0		
Grade 3 Pain, Men C	4	0		
Any Pain, MMRV	78	31		
Grade 3 Pain, MMRV	1	1		
Any Redness, Men C	100	0		
Grade 3 Redness, Men C	9	0		
Any Redness, MMRV	92	41		
Grade 3 Redness, MMRV	4	1		
Any Swelling, Men C	68	0		
Grade 3 Swelling, Men C	9	0		

Any Swelling, MMRV	47	20		
Grade 3 Swelling, MMRV	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general symptoms

End point title	Number of subjects reporting any, grade 3 and related solicited general symptoms
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End point description:

Assessed solicited general symptoms were drowsiness, irritability/fussiness and loss of appetite. Any = occurrence of the symptom regardless of intensity grade or relationship to vaccination. Grade 3 symptom = symptom that prevented normal activity. Related = symptom assessed by the investigator as related to the vaccination.

End point type	Secondary
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End point timeframe:

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

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	177	171	
Units: Subjects				
Any Drowsiness	148	89	56	
Grade 3 Drowsiness	16	12	6	
Related Drowsiness	128	67	46	
Any Irritability/Fussiness	187	104	84	
Grade 3 Irritability/Fussiness	30	13	7	
Related Irritability/Fussiness	158	82	64	
Any Loss of appetite	178	99	60	
Grade 3 Loss of appetite	25	12	5	
Related Loss of appetite	138	75	43	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, grade 3 and related solicited general symptoms

End point title	Number of subjects reporting any, grade 3 and related solicited general symptoms
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End point description:

Assessed solicited general symptoms were Parotid / salivary gland swelling and suspected signs of

meningism / febrile convulsions. Any = occurrence of the symptom regardless of intensity grade or relationship to vaccination. Grade 3 parotid / salivary gland swelling = swelling with accompanying general symptoms and Related = symptom assessed by the investigator as related to the vaccination.

End point type	Secondary
End point timeframe:	
During the 43-day (Days 0-42) post-vaccination period	

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	177	171	
Units: Subjects				
Any Parotid / salivary gland swelling	3	4	0	
Grade 3 Parotid / salivary gland swelling	0	0	0	
Related Parotid / salivary gland swelling	3	3	0	
Any Suspected signs of meningism	1	0	1	
Grade 3 Suspected signs of meningism	0	0	0	
Related Suspected signs of meningism	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting fever per half degree

End point title	Number of subjects reporting fever per half degree
End point description:	
Any fever = fever $\geq 38.0^{\circ}\text{C}$ on rectal setting, grade 3 fever = fever $> 39.5^{\circ}\text{C}$ and related = fever assessed by the investigator as causally related to study vaccination.	
End point type	Secondary
End point timeframe:	
During the 43-day (Days 0-42) post-vaccination period	

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	336	177	171	
Units: Subjects				
Any temperature	159	86	46	
Grade 3 temperature	15	9	4	
Related temperature	178	84	28	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, localised and genralised rashes

End point title	Number of subjects reporting any, localised and genralised rashes
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End point description:

Rash/exanthem was defined as:

1) measles/ rubella rashes (macular or maculo-papular rashes): presence of macules, discolored small patches or spots of the skin, neither elevated nor depressed below the skin's surface.

2) varicella rash (maculo-papulo-vesicular): simultaneous presence of macules, papules and vesicles raised above the skin's surface or other types of rash (heat rash, diaper rash etc.).

Any rash = no lesions and grade 3 = > 150 lesions.

End point type	Secondary
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End point timeframe:

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

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	177	171	
Units: Subjects				
Any, Localised or generalised rash	91	41	15	
Any, With fever rash	59	30	2	
Any, Varicella like rash	6	1	1	
Any, Measles/Rubella like rash	40	16	2	
Any, Grade 3 rash	2	1	2	
Any, Related rash	66	22	6	
Localised, Any rash	43	13	9	
Localised, Administration site rash	3	1	3	
Localised, Other site rash	40	12	6	
Localised, With fever rash	23	10	1	
Localised, Varicella like rash	2	0	0	
Localised, Measles/Rubella like rash	15	3	2	
Localised, Grade 3 rash	0	0	1	
Localised, Related rash	31	4	6	
Generalised, Any rash	54	28	6	
Generalised, With fever rash	38	20	1	
Generalised, Varicella like rash	4	1	1	
Generalised, Measles/Rubella like rash	25	13	0	
Generalised, Grade 3 rash	2	1	1	
Generalised, Related rash	39	18	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any unsolicited adverse events

End point title	Number of subjects with any unsolicited adverse events
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End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product reported in addition to those solicited during the clinical study. Any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary
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End point timeframe:

Within 43 days (Days 0-42) after each vaccination

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	183	182	
Units: Subjects				
Any AE(s)	97	61	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events (SAEs).

End point title	Number of subjects with serious adverse events (SAEs).
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End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary
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End point timeframe:

Throughout study period (from Day 0 to approximately Month 4)

End point values	MMRV + MenC Group	MMRV Group	MenC Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	351	183	182	
Units: Subjects				
Any SAE(s)	6	4	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Antibody titers against measles, mumps, rubella and varicella viruses

End point title	Antibody titers against measles, mumps, rubella and varicella viruses ^[4]
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End point description:

Antibody titers were summarized by geometric mean concentrations (GMCs) with their 95% confidence intervals (CIs)

End point type	Secondary
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End point timeframe:

At Day 42 after vaccination

Notes:

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

Justification: This outcome measure concerns subjects in MMRV + MenC Group and MMRV Group only. Subjects in MMRV Group did not receive MenC vaccine.

End point values	MMRV + MenC Group	MMRV Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309	164		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-measles [N=307, 163]	2943.6 (2691.5 to 3219.2)	3158.5 (2749.7 to 3628)		
Anti-mumps [N=309, 162]	1530.7 (1368.4 to 1712.1)	1591.3 (1346.2 to 1881)		
Anti-rubella [N=309, 164]	40.2 (37.3 to 43.3)	44.9 (40.6 to 49.6)		
Anti- varicella [N= 300, 159]	156.3 (143.9 to 169.8)	145.2 (129.5 to 162.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local & general symptoms were collected during Days 0-3 and Days 0-14 post-vaccination period, respectively. Unsolicited AEs were collected during the 43 day (Days 0-42) post each vaccination. SAEs were collected throughout the entire study period

Adverse event reporting additional description:

The number of occurrences reported for serious adverse events were not available for posting. The number of subjects affected by each specific event was indicated as the number of occurrences.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	MMRV + MenC Group
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Reporting group description:

Subjects who received MenC vaccine co-administered along with MMRV vaccine at Visit 1 (Day 0).

Reporting group title	MMRV Group
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Reporting group description:

Subjects who received MMRV vaccine at Visit 1 (Day 0) and MenC vaccine at Visit 2 (Days 35-49).

Reporting group title	MenC Group
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Reporting group description:

Subjects who received MenC vaccine at Visit 1 (Day 0) and MMRV vaccine at Visit 2 (Days 35-49)

Serious adverse events	MMRV + MenC Group	MMRV Group	MenC Group
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 351 (1.71%)	4 / 183 (2.19%)	2 / 182 (1.10%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Skull fractured base			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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			
Febrile convulsion			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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
Loss of consciousness alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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			
Diarrhoea alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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
Dyspepsia alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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
Stomatitis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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
Musculoskeletal and connective tissue disorders			
Arthritis alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Growth retardation alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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
Infections and infestations			
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	1 / 183 (0.55%)	0 / 182 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 183 (0.55%)	1 / 182 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 351 (0.00%)	1 / 183 (0.55%)	0 / 182 (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
Cellulitis orbital			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 351 (0.00%)	0 / 183 (0.00%)	1 / 182 (0.55%)
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 adenovirus			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 351 (0.28%)	0 / 183 (0.00%)	0 / 182 (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 infection			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 351 (0.00%)	1 / 183 (0.55%)	0 / 182 (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

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

Non-serious adverse events	MMRV + MenC Group	MMRV Group	MenC Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 351 (62.68%)	114 / 183 (62.30%)	84 / 182 (46.15%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	148 / 351 (42.17%)	89 / 183 (48.63%)	56 / 182 (30.77%)
occurrences (all)	148	89	56
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	92 / 351 (26.21%)	31 / 183 (16.94%)	0 / 182 (0.00%)
occurrences (all)	92	31	0
Injection site swelling			
subjects affected / exposed	79 / 351 (22.51%)	20 / 183 (10.93%)	1 / 182 (0.55%)
occurrences (all)	79	20	1
Injection site erythema			
subjects affected / exposed	121 / 351 (34.47%)	41 / 183 (22.40%)	0 / 182 (0.00%)
occurrences (all)	121	41	0
Decreased appetite			
subjects affected / exposed	178 / 351 (50.71%)	99 / 183 (54.10%)	60 / 182 (32.97%)
occurrences (all)	178	99	60
Irritability postvaccinal			
subjects affected / exposed	187 / 351 (53.28%)	104 / 183 (56.83%)	84 / 182 (46.15%)
occurrences (all)	187	104	84
Pyrexia			
subjects affected / exposed	220 / 351 (62.68%)	114 / 183 (62.30%)	64 / 182 (35.16%)
occurrences (all)	220	114	64
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	11 / 351 (3.13%) 12	10 / 183 (5.46%) 10	4 / 182 (2.20%) 4
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	11 / 351 (3.13%) 11	10 / 183 (5.46%) 10	5 / 182 (2.75%) 5
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	91 / 351 (25.93%) 91	41 / 183 (22.40%) 41	15 / 182 (8.24%) 15
Infections and infestations Pharyngitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	16 / 351 (4.56%) 16	10 / 183 (5.46%) 10	9 / 182 (4.95%) 10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2012	<p>Rationale for amendment: The period of recruitment was extended from 3 to 6 months. Reporting of local solicited AEs and reporting of unsolicited AEs after vaccination at Visit 2 was not collected, because the vaccinations administered at Visit 2 were not considered as study vaccines.</p>
24 September 2012	<p>Rationale for amendment: Change made in the estimated sample size which was decreased from the initially estimated 808 subjects to 720 subjects. This change was made since the study sites were not able to recruit the initially estimated target population during the planned study period, due to the following reason: In November 2011, the Italian National Drug Agency (Agenzia Italiana del Farmaco [AIFA]) released a recommendation on the varicella vaccination strategy. The recommendation strongly discouraged the administration of measles mumps rubella varicella vaccine (MMRV) (Priorix Tetra) as the first dose and was in favour of the concomitant administration of the measles mumps rubella vaccine (MMR) and the monovalent varicella vaccine (V), due to the higher risk of febrile convulsions associated with the former. A section of paediatricians and health care providers (HCPs) prefer the MMR+V immunization strategy as compared to the MMRV immunization strategy. The recommendation had affected the recruitment rate of this study and a lower recruitment rate of subjects as compared to the recruitment rate forecasted based on the study feasibility activities (carried out before November 2011), was observed. The reduction in sample size from 808 subjects to 720 subjects was made keeping in mind that it provided sufficient power to answer the study objectives (to allow consistent comparison among the study arms), as the results of this study are of value to the countries/HCPs that plan to administer MMRV+ meningococcal C (MenC) vaccines concomitantly.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported