



## Clinical trial results:

### A Phase III Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Safety, Tolerability, and Immunogenicity of Measles, Mumps, Rubella, Varicella (MMRV) Vaccine Made with an Alternative Manufacturing Process (AMP)

#### Summary

EudraCT number	2017-001443-13
Trial protocol	Outside EU/EEA
Global end of trial date	27 January 2014

#### Results information

Result version number	v1 (current)
This version publication date	15 June 2017
First version publication date	15 June 2017

#### Trial information

##### Trial identification

Sponsor protocol code	V221-027
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01536405
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	27 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 January 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This study compared the safety, tolerability, and immunogenicity of measles, mumps, rubella, and varicella (MMRV) vaccine made with an alternative manufacturing process (MMRV [AMP]) with those of ProQuad™ (MMRV [2006 Process]). The primary hypothesis of the study was that MMRV (AMP) induces measles, mumps, rubella, and VZV antibody responses 6 weeks Postdose 1 that are non-inferior to those induced by MMRV (2006 Process).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 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	United States: 1412
Worldwide total number of subjects	1412
EEA total number of subjects	0

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)	1412
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
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## Subject disposition

### Recruitment

Recruitment details:

The study enrolled healthy children 12- to 23-months of age with no clinical history for measles, mumps, rubella, varicella, or zoster.

### Pre-assignment

Screening details:

One participant was inadvertently randomized twice, for a total of 1413 randomizations. The Subject Disposition tables below include this participant only once.

### Period 1

Period 1 title	Randomization to Visit 1 (Day 1)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MMRV (AMP)

Arm description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Arm type	Experimental
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process.
Investigational medicinal product code	
Other name	V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Arm title</b>	MMRV (2006 Process)
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Arm description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Arm type	Active comparator
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process.
Investigational medicinal product code	
Other name	ProQuad™ V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

Number of subjects in period 1	MMRV (AMP)	MMRV (2006 Process)
Started	706	706
Completed	698	702
Not completed	8	4
Not vaccinated	8	4

## Period 2

Period 2 title	Visit 1 (Day 1) to Visit 2 (Day 43)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MMRV (AMP)

### Arm description:

Participants were to receive two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Arm type	Experimental
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process.
Investigational medicinal product code	
Other name	V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Arm title</b>	MMRV (2006 Process)
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### Arm description:

Participants were to receive two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Arm type	Active comparator
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process.
Investigational medicinal product code	
Other name	ProQuad™ V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

### Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

Number of subjects in period 2	MMRV (AMP)	MMRV (2006 Process)
Started	698	702
Received Vaccination 1	698	702
Completed	666	662
Not completed	32	40
Consent withdrawn by subject	12	18
Lost to follow-up	20	22

### Period 3

Period 3 title	Visit 2 (Day 43) to Visit 3 (Day 91)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MMRV (AMP)

#### Arm description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Arm type	Experimental
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process.
Investigational medicinal product code	
Other name	V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

#### Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Arm title</b>	MMRV (2006 Process)
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#### Arm description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Arm type	Active comparator
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process.
Investigational medicinal product code	
Other name	ProQuad™ V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

#### Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

Number of subjects in period 3	MMRV (AMP)	MMRV (2006 Process)
Started	666	662
Completed	635	634
Not completed	31	28
Consent withdrawn by subject	17	13
Adverse event, non-fatal	3	3
Lost to follow-up	9	10
Protocol deviation	2	2

#### Period 4

Period 4 title	Visit 3 (Day 91) to Visit 4 (Day 133)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

#### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MMRV (AMP)

#### Arm description:

Participants were to receive two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Arm type	Experimental
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process.
Investigational medicinal product code	
Other name	V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

#### Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Arm title</b>	MMRV (2006 Process)
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#### Arm description:

Participants were to receive two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Arm type	Active comparator
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process.
Investigational medicinal product code	
Other name	ProQuad™ V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Number of subjects in period 4</b>	MMRV (AMP)	MMRV (2006 Process)
Started	635	634
Received Vaccination 2	634	632
Completed	615	618
Not completed	20	16
Consent withdrawn by subject	3	2
Adverse event, non-fatal	1	-
Lost to follow-up	16	14

**Period 5**

Period 5 title	Visit 4 (Day 133) to Visit 5 (Day 271)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

**Arms**

Are arms mutually exclusive?	Yes
<b>Arm title</b>	MMRV (AMP)

**Arm description:**

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Arm type	Experimental
Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process.
Investigational medicinal product code	
Other name	V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

**Dosage and administration details:**

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Arm title</b>	MMRV (2006 Process)
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**Arm description:**

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Arm type	Active comparator
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Investigational medicinal product name	Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process.
Investigational medicinal product code	
Other name	ProQuad™ V221
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Two 0.5 mL subcutaneous injections administered at Day 1 and Day 91

<b>Number of subjects in period 5</b>	MMRV (AMP)	MMRV (2006 Process)
Started	615	618
Completed	595	595
Not completed	20	23
Consent withdrawn by subject	-	2
Adverse event, non-fatal	-	1
Lost to follow-up	20	20

## Baseline characteristics

### Reporting groups

Reporting group title	MMRV (AMP)
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Reporting group description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Reporting group title	MMRV (2006 Process)
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Reporting group description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Reporting group values	MMRV (AMP)	MMRV (2006 Process)	Total
Number of subjects	706	706	1412
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	706	706	1412
Age Continuous Units: months			
arithmetic mean	13.4	13.6	
standard deviation	± 2.2	± 2.5	-
Gender Categorical Units: Subjects			
Female	344	324	668
Male	362	382	744

## End points

### End points reporting groups

Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Reporting group title	MMRV (AMP)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])	
Reporting group title	MMRV (2006 Process)
Reporting group description: Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])	
Subject analysis set title	MMRV (AMP) - Received at Least One Vaccination
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received at least one 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella (MMRV) vaccine made with an alternative manufacturing process (AMP)	
Subject analysis set title	MMRV (2006 Process) - Received at Least one Vaccination
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received at least one 0.5 mL subcutaneous injections of MMRV made with the 2006 manufacturing process	

**Primary: Percentage of Participants With Varicella Zoster Virus (VZV) Antibody Levels  $\geq 5$  gpELISA Units/mL**

End point title	Percentage of Participants With Varicella Zoster Virus (VZV) Antibody Levels $\geq 5$ gpELISA Units/mL
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End point description:

Sera were tested for VZV Immunoglobulin (IgG) antibody levels by a glycoprotein enzyme-linked immunosorbent assay (gpELISA). The population analyzed included participants who received  $\geq 1$  dose of study vaccine, were seronegative at baseline and had postvaccination VZV serology results.

End point type	Primary
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End point timeframe:

Six weeks after vaccination 1

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	586	589		
Units: Percentage of participants				
number (confidence interval 95%)	97.3 (95.6 to 98.4)	93 (90.7 to 95)		

**Statistical analyses**

<b>Statistical analysis title</b>	Non-inferiority Analysis
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Statistical analysis description:

The non-inferiority evaluation is based on the lower bound of the 2-sided 95% confidence interval (CI) on the risk difference excluding a decrease  $\geq$  the prespecified criterion of 10 percentage points.

Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
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Number of subjects included in analysis	1175
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Analysis specification	Pre-specified
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Analysis type	non-inferiority <sup>[1]</sup>
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P-value	$< 0.001$
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Method	Miettinen and Nurminen
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Parameter estimate	Risk difference (RD)
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Point estimate	4.2
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	1.8
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upper limit	6.8
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Notes:

[1] - Risk Difference = MMRV (AMP) - MMRV (2006 process)

**Primary: Percentage of Participants With Measles Virus Antibody Levels  $\geq 255$  mIU/mL**

End point title	Percentage of Participants With Measles Virus Antibody Levels
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>=255 mIU/mL

End point description:

Sera were tested for measles virus IgG antibody levels by an ELISA. The population analyzed included participants who received >=1 dose of study vaccine, were seronegative at baseline and had postvaccination measles virus serology results.

End point type Primary

End point timeframe:

Six weeks after vaccination 1

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	629	621		
Units: Percentage of participants				
number (confidence interval 95%)	96.7 (94.9 to 97.9)	98.9 (97.7 to 99.5)		

## Statistical analyses

Statistical analysis title Non-inferiority Analysis

Statistical analysis description:

The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease >= the prespecified criterion of 5 percentage points.

Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1250
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
P-value	= 0.003
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	-0.6

Notes:

[2] - Risk Difference = MMRV (AMP) - MMRV (2006 process)

## Primary: Percentage of Participants With Mumps Virus Antibody Levels >=10 Mumps Ab Units/mL

End point title Percentage of Participants With Mumps Virus Antibody Levels >=10 Mumps Ab Units/mL

End point description:

Sera were tested for mumps virus IgG antibody levels by an enzyme-linked immunosorbent assay

(ELISA). The population analyzed included participants who received  $\geq 1$  dose of study vaccine, were seronegative at baseline and had postvaccination mumps virus serology results.

End point type	Primary
End point timeframe:	
Six weeks after vaccination 1	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	618	610		
Units: Percentage of participants				
number (confidence interval 95%)	98.2 (96.8 to 99.1)	97.2 (95.6 to 98.4)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease $\geq$ the prespecified criterion of 5 percentage points.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1228
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	2.8

Notes:

[3] - Risk Difference = MMRV (AMP) - MMRV (2006 process)

## Primary: Percentage of Participants With Rubella Virus Antibody Levels $\geq 10$ International Units/mL (IU/mL)

End point title	Percentage of Participants With Rubella Virus Antibody Levels $\geq 10$ International Units/mL (IU/mL)
End point description:	
Sera were tested for rubella virus IgG antibody levels by an ELISA. The population analyzed included participants who received $\geq 1$ dose of study vaccine, were seronegative at baseline and had postvaccination rubella serology results.	
End point type	Primary

End point timeframe:

Six weeks after vaccination 1

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	608	593		
Units: Percentage of participants				
number (confidence interval 95%)	98.8 (97.6 to 99.5)	99.3 (98.3 to 99.8)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
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Statistical analysis description:

The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease  $\geq$  the prespecified criterion of 5 percentage points.

Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1201
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[4]</sup>
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.7

Notes:

[4] - Risk Difference = MMRV (AMP) - MMRV (2006 process)

## Primary: Geometric Mean Titer (GMT) of VZV Antibodies

End point title	Geometric Mean Titer (GMT) of VZV Antibodies
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End point description:

Sera were tested for VZV IgG antibody levels by gpELISA. The population analyzed included participants who received  $\geq 1$  dose of study vaccine, were seronegative at baseline and had postvaccination VZV serology results.

End point type	Primary
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End point timeframe:

Six weeks after vaccination 1

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	586	589		
Units: gpELISA Units/mL				
geometric mean (confidence interval 95%)	17.3 (16.4 to 18.3)	14.4 (13.6 to 15.2)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the GMT ratio, excluding a decrease of $\geq 1.5$ fold. Analysis was based on log-transformed titers.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1175
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	GMT Ratio
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.3

Notes:

[5] - GMT ratio = MMRV (AMP) / MMRV (2006 process).

## Primary: Geometric Mean Titer (GMT) of Measles Virus Antibodies

End point title	Geometric Mean Titer (GMT) of Measles Virus Antibodies
End point description:	
Sera were tested for measles virus IgG antibody levels by ELISA. The population analyzed included participants who received $\geq 1$ dose of study vaccine, were seronegative at baseline and had postvaccination measles virus serology results.	
End point type	Primary
End point timeframe:	
Six weeks after vaccination 1	



End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	629	621		
Units: mIU/mL				
geometric mean (confidence interval 95%)	3426.5 (3162.5 to 3712.4)	3719.5 (3506 to 3946)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the GMT ratio, excluding a decrease of $\geq 1.5$ fold. Analysis was based on log-transformed titers.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1250
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[6]</sup>
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	GMT Ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1

Notes:

[6] - GMT ratio = MMRV (AMP) / MMRV (2006 process).

## Primary: Geometric Mean Titer (GMT) of Mumps Virus Antibodies

End point title	Geometric Mean Titer (GMT) of Mumps Virus Antibodies
End point description:	
Sera were tested for mumps virus IgG antibody levels by ELISA. The population analyzed included participants who received $\geq 1$ dose of study vaccine, were seronegative at baseline and had postvaccination mumps virus serology results.	
End point type	Primary
End point timeframe:	
Six weeks after vaccination 1	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	618	610		
Units: Mumps Ab units/mL				
geometric mean (confidence interval 95%)	112.1 (104.1 to 120.7)	114 (105.8 to 122.8)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the GMT ratio, excluding a decrease of $\geq 1.5$ fold. Analysis was based on log-transformed titers.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1228
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	GMT Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.1

Notes:

[7] - GMT ratio = MMRV (AMP) / MMRV (2006 process).

## Primary: Geometric Mean Titer (GMT) of Rubella Virus Antibodies

End point title	Geometric Mean Titer (GMT) of Rubella Virus Antibodies
End point description:	
Sera were tested for rubella virus IgG antibody levels by ELISA. The population analyzed included participants who received $\geq 1$ dose of study vaccine, were seronegative at baseline and had postvaccination rubella virus serology results.	
End point type	Primary
End point timeframe:	
Six weeks after vaccination 1	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	608	593		
Units: IU/mL				
geometric mean (confidence interval 95%)	81.8 (76.8 to 87.2)	80.7 (76.4 to 85.2)		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the lower bound of the 2-sided 95% CI on the GMT ratio, excluding a decrease of $\geq 1.5$ fold. Analysis was based on log-transformed titers.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1201
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[8]</sup>
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	GMT Ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.1

Notes:

[8] - GMT ratio = MMRV (AMP) / MMRV (2006 process).

## Primary: Percentage of Participants With Fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or Oral Equivalent)

End point title	Percentage of Participants With Fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or Oral Equivalent)
End point description:	
Daily temperatures were recorded using a standardized Vaccination Report Card (VRC). The percentage of participants with fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or oral equivalent) was assessed. The population analyzed included participants who received $\geq 1$ study vaccination and had follow-up safety data.	
End point type	Primary
End point timeframe:	
Up to 5 days after vaccination 1	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	645	648		
Units: Percentage of participants				
number (not applicable)	0.9	0.8		

## Statistical analyses

Statistical analysis title	Non-inferiority Analysis
Statistical analysis description:	
The non-inferiority evaluation is based on the upper bound of the 2-sided 95% CI on the risk difference excluding an increase $\geq$ the prespecified criterion of 5 percentage points.	
Comparison groups	MMRV (AMP) - Received at Least One Vaccination v MMRV (2006 Process) - Received at Least one Vaccination
Number of subjects included in analysis	1293
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[9]</sup>
P-value	$< 0.001$
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.3

Notes:

[9] - Risk Difference = MMRV (AMP) - MMRV (2006 process)

## Secondary: Percentage of Participants With Fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or Oral Equivalent)

End point title	Percentage of Participants With Fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or Oral Equivalent)
End point description:	
Daily temperatures were recorded using a standardized VRC. The percentage of participants with fever ( $\geq 102.2^{\circ}\text{F}$ [ $39.0^{\circ}\text{C}$ ] or oral equivalent) was assessed. The population analyzed included participants who received $\geq 1$ study vaccination and had follow-up safety data.	
End point type	Secondary
End point timeframe:	
Up to 42 days after each vaccination	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	650	649		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=650, 649	10	10.6		
Vaccination 2: n=592, 597	5.7	8.4		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Zoster-like Rash

End point title	Percentage of Participants With Zoster-like Rash
End point description: Zoster-like rash was solicited on the standardized VRC. The percentage of participants with zoster-like rash was assessed. The population analyzed included participants who received $\geq 1$ study vaccination and had follow-up safety data.	
End point type	Secondary
End point timeframe: Up to 42 days after each vaccination	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	0	0		
Vaccination 2: n=634, 632	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Mumps-like Symptoms

End point title	Percentage of Participants With Mumps-like Symptoms
End point description: Mumps-like symptoms were solicited on the standardized VRC. The percentage of participants with mumps-like symptoms was assessed. The population analyzed included participants who received $\geq 1$	

study vaccination and had follow-up safety data.

End point type	Secondary
End point timeframe:	
Up to 42 days after each vaccination	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	0	0		
Vaccination 2: n=634, 632	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Measles-like Rash

End point title	Percentage of Participants With Measles-like Rash
End point description:	
Measles-like rash was solicited on the standardized VRC. The percentage of participants with measles-like rash was assessed. The population analyzed included participants who received $\geq 1$ study vaccination and had follow-up safety data.	
End point type	Secondary
End point timeframe:	
Up to 42 days after each vaccination	

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	0.1	0.3		
Vaccination 2: n=634, 632	0.2	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Rubella-like Rash

End point title	Percentage of Participants With Rubella-like Rash
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End point description:

Rubella-like rash was solicited on the standardized VRC. The percentage of participants with rubella-like rash was assessed. The population analyzed included participants who received  $\geq 1$  study vaccination and had follow-up safety data.

End point type	Secondary
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End point timeframe:

Up to 42 days after each vaccination

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	0	0		
Vaccination 2: n=634, 632	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Varicella-like Rash

End point title	Percentage of Participants With Varicella-like Rash
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End point description:

Varicella-like rash was solicited on the standardized VRC. The percentage of participants with varicella-like rash was assessed. The population analyzed included participants who received  $\geq 1$  study vaccination and had follow-up safety data.

End point type	Secondary
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End point timeframe:

Up to 42 days after each vaccination

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	0.6	0		
Vaccination 2; n=634, 632	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With an Injection-site Adverse Event

End point title	Percentage of Participants With an Injection-site Adverse Event
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End point description:

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. Injection-site AEs were solicited on the standardized VRC. The percentage of participants with a VRC-solicited injection-site AE was assessed. The population analyzed included participants who received  $\geq 1$  study vaccination and had follow-up safety data.

End point type	Secondary
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End point timeframe:

Up to 5 days after each vaccination

End point values	MMRV (AMP) - Received at Least One Vaccination	MMRV (2006 Process) - Received at Least one Vaccination		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	682	682		
Units: Percentage of participants				
number (not applicable)				
Vaccination 1: n=682, 682	36.4	29.8		
Vaccination 2: n=634, 632	35.5	29.6		

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 6 months (180 days) after vaccination 2

Adverse event reporting additional description:

The population analyzed included randomized participants who received  $\geq 1$  dose of study vaccine and had safety follow-up results.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16
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### Reporting groups

Reporting group title	MMRV (2006 Process)
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Reporting group description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with the 2006 manufacturing process (MMRV [2006 Process])

Reporting group title	MMRV (AMP)
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Reporting group description:

Participants were to received two 0.5 mL subcutaneous injections of Mumps, Measles, Rubella, Varicella vaccine made with an alternative manufacturing process (MMRV [AMP])

Serious adverse events	MMRV (2006 Process)	MMRV (AMP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 683 (2.64%)	21 / 682 (3.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Exposure via direct contact			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exposure via ingestion			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body aspiration			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skull fracture			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Kawasaki's disease			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 683 (0.15%)	4 / 682 (0.59%)	
occurrences causally related to treatment / all	1 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 683 (0.44%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			

subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	2 / 683 (0.29%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Croup infectious			
subjects affected / exposed	2 / 683 (0.29%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 683 (0.00%)	2 / 682 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	2 / 683 (0.29%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 683 (0.15%)	0 / 682 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 683 (0.15%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 683 (0.00%)	2 / 682 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 683 (0.00%)	1 / 682 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MMRV (2006 Process)	MMRV (AMP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	572 / 683 (83.75%)	574 / 682 (84.16%)	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	187 / 683 (27.38%)	208 / 682 (30.50%)	
occurrences (all)	243	267	
Injection site erythema			
subjects affected / exposed	199 / 683 (29.14%)	254 / 682 (37.24%)	
occurrences (all)	258	344	
Pyrexia			
subjects affected / exposed	235 / 683 (34.41%)	225 / 682 (32.99%)	
occurrences (all)	360	349	
Injection site swelling			
subjects affected / exposed	123 / 683 (18.01%)	156 / 682 (22.87%)	
occurrences (all)	146	190	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	46 / 683 (6.73%)	48 / 682 (7.04%)	
occurrences (all)	47	52	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	91 / 683 (13.32%)	77 / 682 (11.29%)	
occurrences (all)	107	98	
Vomiting			

subjects affected / exposed occurrences (all)	61 / 683 (8.93%) 72	60 / 682 (8.80%) 77	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	53 / 683 (7.76%)	58 / 682 (8.50%)	
occurrences (all)	64	78	
Cough			
subjects affected / exposed	101 / 683 (14.79%)	87 / 682 (12.76%)	
occurrences (all)	118	113	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	77 / 683 (11.27%)	62 / 682 (9.09%)	
occurrences (all)	106	76	
Rash			
subjects affected / exposed	47 / 683 (6.88%)	48 / 682 (7.04%)	
occurrences (all)	55	50	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	41 / 683 (6.00%)	29 / 682 (4.25%)	
occurrences (all)	43	32	
Otitis media acute			
subjects affected / exposed	44 / 683 (6.44%)	56 / 682 (8.21%)	
occurrences (all)	57	72	
Nasopharyngitis			
subjects affected / exposed	66 / 683 (9.66%)	55 / 682 (8.06%)	
occurrences (all)	76	65	
Otitis media			
subjects affected / exposed	128 / 683 (18.74%)	128 / 682 (18.77%)	
occurrences (all)	179	177	
Pharyngitis			
subjects affected / exposed	35 / 683 (5.12%)	40 / 682 (5.87%)	
occurrences (all)	43	47	
Viral infection			
subjects affected / exposed	57 / 683 (8.35%)	44 / 682 (6.45%)	
occurrences (all)	64	52	
Upper respiratory tract infection			

subjects affected / exposed	163 / 683 (23.87%)	159 / 682 (23.31%)	
occurrences (all)	212	210	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2012	Amendment 1: The amendment incorporated a new primary objective for safety and a new co-primary hypothesis for immunogenicity.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported