



## Clinical trial results:

### A Phase III Double Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety and Tolerability of VARIVAX™ New Seed Process (NSP) Administered Concomitantly with M-M-R™ II

#### Summary

EudraCT number	2017-001444-35
Trial protocol	Outside EU/EEA
Global end of trial date	13 October 2015

#### Results information

Result version number	v1 (current)
This version publication date	17 June 2017
First version publication date	17 June 2017

#### Trial information

##### Trial identification

Sponsor protocol code	V210-063
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02062502
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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	13 October 2015
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	13 October 2015
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

This study evaluated the immunogenicity, safety, and tolerability of VARIVAX™ (Varicella Virus Vaccine Live) manufactured with a New Seed Process (NSP) compared with the VARIVAX™ 2007 process. The primary hypothesis tested was that antibody response rate and mean antibody titer induced at 6 weeks after a single vaccination by VARIVAX™ NSP are non-inferior to those induced by VARIVAX™ 2007 process.

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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.

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Background therapy: -

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Evidence for comparator: -

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Actual start date of recruitment	07 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United States: 611
Worldwide total number of subjects	611
EEA total number of subjects	0

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Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	611
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

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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 who had not received measles, mumps, rubella, or varicella vaccine.

### Pre-assignment

Screening details:

A total of 654 participants were screened and 611 were enrolled in the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	VARIVAX™ New Seed Process + M-M-R II™
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Arm description:

VARIVAX™ New Seed Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91

Arm type	Experimental
Investigational medicinal product name	VARIVAX™ New Seed Process
Investigational medicinal product code	
Other name	Varicella Virus Vaccine Live
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.

Investigational medicinal product name	M-M-R II™ for Co-administration
Investigational medicinal product code	
Other name	Measles, Mumps, and Rubella Virus Vaccine Live
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL administered in the left arm by subcutaneous injection on Day 1 and Day 91.

<b>Arm title</b>	VARIVAX™ 2007 Process + M-M-R II™
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Arm description:

VARIVAX™ 2007 Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.

Arm type	Active comparator
Investigational medicinal product name	VARIVAX™ 2007 Process
Investigational medicinal product code	
Other name	Varicella Virus Vaccine Live
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL administered in the left arm by subcutaneous injection on Day 1 and Day 91.

Investigational medicinal product name	M-M-R II™ for Co-administration
Investigational medicinal product code	
Other name	Measles, Mumps, and Rubella Virus Vaccine Live
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.

<b>Number of subjects in period 1</b>	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™
Started	306	305
Vaccinated Dose 1	306	305
Completed	263	270
Not completed	43	35
Physician decision	-	1
Death	-	1
Lost to follow-up	18	14
Withdrawal by parent/guardian	22	18
Protocol deviation	3	1

## Baseline characteristics

### Reporting groups

Reporting group title	VARIVAX™ New Seed Process + M-M-R II™
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Reporting group description:

VARIVAX™ New Seed Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91

Reporting group title	VARIVAX™ 2007 Process + M-M-R II™
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Reporting group description:

VARIVAX™ 2007 Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.

Reporting group values	VARIVAX™ New Seed Process + M-M-R II™	VARIVAX™ 2007 Process + M-M-R II™	Total
Number of subjects	306	305	611
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	306	305	611
Age Continuous Units: months			
arithmetic mean	12.9	12.8	
standard deviation	± 1.9	± 1.7	-
Gender Categorical Units: Subjects			
Female	140	139	279
Male	166	166	332

## End points

### End points reporting groups

Reporting group title	VARIVAX™ New Seed Process + M-M-R II™
Reporting group description: VARIVAX™ New Seed Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91	
Reporting group title	VARIVAX™ 2007 Process + M-M-R II™
Reporting group description: VARIVAX™ 2007 Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.	

### Primary: Percentage of Participants With Varicella Zoster Virus (VZV) Antibody Levels $\geq 5$ Glycoprotein Enzyme-linked Immunosorbent Assay (gpELISA) Units/mL

End point title	Percentage of Participants With Varicella Zoster Virus (VZV) Antibody Levels $\geq 5$ Glycoprotein Enzyme-linked Immunosorbent Assay (gpELISA) Units/mL
End point description: Anti-VZV antibody levels were measured using a gpELISA assay. The percentage of participants with antibody levels $\geq 5$ gpELISA Units/mL was assessed. The analysis population was participants with a seronegative antibody titer at baseline and postvaccination serology contributing to the per-protocol analysis.	
End point type	Primary
End point timeframe: 6 weeks (43 days) after vaccination 1	

End point values	VARIVAX™ New Seed Process + M-M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	254		
Units: Percentage of participants				
number (confidence interval 95%)	97.2 (94.4 to 98.9)	97.2 (94.4 to 98.9)		

### Statistical analyses

Statistical analysis title	Risk Difference in Response Rates
Statistical analysis description: The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease equal to or more than the prespecified criterion of 10.0 percentage points for Varicella zoster virus.	
Comparison groups	VARIVAX™ New Seed Process + M-M-R II™ v VARIVAX™ 2007 Process + M-M-R II™

Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	3.2

### Primary: Geometric Mean Titer of VZV Antibodies

End point title	Geometric Mean Titer of VZV Antibodies
End point description:	Anti-VZV antibody levels were measured using a gpELISA assay. The Geometric Mean Titer was assessed. The analysis population was participants with a seronegative antibody titer at baseline and postvaccination serology contributing to the per-protocol analysis.
End point type	Primary
End point timeframe:	6 weeks (43 days) after vaccination 1

End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	254		
Units: gpELISA units/mL				
geometric mean (confidence interval 95%)	16.3 (15.1 to 17.6)	17.2 (15.8 to 18.7)		

### Statistical analyses

Statistical analysis title	Non-inferiority
Statistical analysis description:	The conclusion of non-inferiority (similarity) is based on the lower bound of the 2-sided 95% CI on fold-difference, excluding a decrease of 1.5 fold or more.
Comparison groups	VARIVAX™ New Seed Process + M-M-R II™ v VARIVAX™ 2007 Process + M-M-R II™



Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	GMT Ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.06

### Secondary: Percentage of Participants With Fever ( $\geq 102.2$ °F Oral Equivalent)

End point title	Percentage of Participants With Fever ( $\geq 102.2$ °F Oral Equivalent)
End point description:	Daily temperatures were recorded using a standardized Vaccination Report Card (VRC). The percentage of participants with fever ( $\geq 102.2$ °F oral equivalent) was assessed. The analysis population is All Subjects as Treated with results after Vaccination 1 or 2.
End point type	Secondary
End point timeframe:	Up to 42 days after Vaccination 1 and Vaccination 2 (up to 133 days)

End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	293		
Units: Percentage of participants				
number (not applicable)				
Up to 42 days after Vaccination 1: n=285, 287	9.5	10.5		
Up to 42 days after Vaccination 2: n=258, 267	8.1	8.6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Systemic Measles-like, Rubella-like, Varicella-like Rash, Mumps-like Symptoms, and Injection-site Rash After Vaccination 1

End point title	Percentage of Participants With Systemic Measles-like, Rubella-like, Varicella-like Rash, Mumps-like Symptoms, and Injection-site Rash After Vaccination 1
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End point description:

The development of varicella-like, herpes zoster-like, measles-like and rubella-like rashes and mumps-like symptoms was recorded on the VRC. The analysis population is All Subjects as Treated with results after Vaccination 1.

End point type	Secondary
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End point timeframe:

Up to 42 days after Vaccination 1

End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	293		
Units: Percentage of participants number (not applicable)				
Measles-like rash	0.3	2.4		
Mumps-like symptoms	0	0		
Rubella-like rash	0	0		
Varicella-like rash	0	0.3		
Zoster-like rash	0	0		
Injection-site rash	0.3	1.4		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Systemic Measles-like, Rubella-like, Varicella-like Rash, Mumps-like Symptoms, and Injection-site Rash After Vaccination 2

End point title	Percentage of Participants With Systemic Measles-like, Rubella-like, Varicella-like Rash, Mumps-like Symptoms, and Injection-site Rash After Vaccination 2
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End point description:

The development of varicella-like, herpes zoster-like, measles-like and rubella-like rashes and mumps-like symptoms was recorded on the VRC. The analysis population is All Subjects as Treated with results after Vaccination 2.

End point type	Secondary
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End point timeframe:

Up to 42 days after Vaccination 2

End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	276		
Units: Percentage of participants				
number (not applicable)				
Measles-like rash	0	0		
Mumps-like symptoms	0	0		
Rubella-like rash	0	0		
Varicella-like rash	0.4	0		
Zoster-like rash	0	0		
Injection-site rash	0.7	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Solicited Injection-site Erythema, Injection-site Swelling, and Injection-site Pain/Tenderness After Vaccination 1

End point title	Percentage of Participants With Solicited Injection-site Erythema, Injection-site Swelling, and Injection-site Pain/Tenderness After Vaccination 1
End point description:	The development of injection-site erythema, swelling, and pain/tenderness was recorded on the VRC. The analysis population is All Subjects as Treated with results after Vaccination 1.
End point type	Secondary
End point timeframe:	Up to 5 days after Vaccination 1

End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	293		
Units: Percentage of participants				
number (not applicable)				
Injection-site erythema	20.3	19.8		
Injection-site swelling	10	10.6		
Injection-site pain/tenderness	29.9	28		

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of Participants With Solicited Injection-site Erythema, Injection-site Swelling, and Injection-site Pain/Tenderness After Vaccination 2**

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End point title	Percentage of Participants With Solicited Injection-site Erythema, Injection-site Swelling, and Injection-site Pain/Tenderness After Vaccination 2
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End point description:

The development of injection-site erythema, swelling, and pain/tenderness was recorded on the VRC. The analysis population is All Subjects as Treated with results after Vaccination 2.

End point type	Secondary
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End point timeframe:

Up to 5 days after Vaccination 2

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End point values	VARIVAX™ New Seed Process + M- M-R II™	VARIVAX™ 2007 Process + M-M-R II™		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	276		
Units: Percentage of participants				
number (not applicable)				
Injection-site erythema	20.6	22.5		
Injection-site swelling	16.2	12		
Injection-site pain/tenderness	22.4	24.3		

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs: up to Day 271; Other AEs: up to 42 days after vaccination 1 or 2, injection-site AEs up to 5 days after vaccination 1 or 2

Adverse event reporting additional description:

The safety population is All Subjects as Treated with safety results.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	VARIVAX™ 2007 Process + M-M-R II™
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Reporting group description:

VARIVAX™ 2007 Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91.

Reporting group title	VARIVAX™ New Seed Process + M-M-R II™
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Reporting group description:

VARIVAX™ New Seed Process 0.5 mL administered in the left arm and M-M-R II™ vaccine 0.5 mL administered in the right arm by subcutaneous injection on Day 1 and Day 91

Serious adverse events	VARIVAX™ 2007 Process + M-M-R II™	VARIVAX™ New Seed Process + M-M-R II™	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 293 (3.07%)	6 / 291 (2.06%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Drowning			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	0 / 293 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (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 / 293 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	3 / 293 (1.02%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 293 (0.00%)	2 / 291 (0.69%)	
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 / 293 (0.34%)	0 / 291 (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	0 / 293 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (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 / 293 (0.00%)	1 / 291 (0.34%)	
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	1 / 293 (0.34%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 293 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 293 (0.34%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 293 (0.00%)	1 / 291 (0.34%)	
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 %

<b>Non-serious adverse events</b>	VARIVAX™ 2007 Process + M-M-R II™	VARIVAX™ New Seed Process + M-M-R II™	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 293 (76.45%)	225 / 291 (77.32%)	
General disorders and administration site conditions			

Injection site erythema subjects affected / exposed occurrences (all)	94 / 293 (32.08%) 190	95 / 291 (32.65%) 181	
Injection site pain subjects affected / exposed occurrences (all)	117 / 293 (39.93%) 270	106 / 291 (36.43%) 272	
Injection site swelling subjects affected / exposed occurrences (all)	59 / 293 (20.14%) 96	61 / 291 (20.96%) 110	
Pyrexia subjects affected / exposed occurrences (all)	60 / 293 (20.48%) 87	60 / 291 (20.62%) 86	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	22 / 293 (7.51%) 25	37 / 291 (12.71%) 42	
Vomiting subjects affected / exposed occurrences (all)	18 / 293 (6.14%) 21	28 / 291 (9.62%) 34	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	25 / 293 (8.53%) 29	18 / 291 (6.19%) 20	
Nasal congestion subjects affected / exposed occurrences (all)	17 / 293 (5.80%) 18	9 / 291 (3.09%) 9	
Rhinorrhoea subjects affected / exposed occurrences (all)	26 / 293 (8.87%) 35	31 / 291 (10.65%) 37	
Skin and subcutaneous tissue disorders			
Dermatitis diaper subjects affected / exposed occurrences (all)	27 / 293 (9.22%) 30	25 / 291 (8.59%) 28	
Rash subjects affected / exposed occurrences (all)	14 / 293 (4.78%) 14	23 / 291 (7.90%) 27	



Psychiatric disorders			
Irritability			
subjects affected / exposed	13 / 293 (4.44%)	17 / 291 (5.84%)	
occurrences (all)	18	18	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	15 / 293 (5.12%)	12 / 291 (4.12%)	
occurrences (all)	15	12	
Otitis media			
subjects affected / exposed	33 / 293 (11.26%)	35 / 291 (12.03%)	
occurrences (all)	36	38	
Otitis media acute			
subjects affected / exposed	14 / 293 (4.78%)	23 / 291 (7.90%)	
occurrences (all)	16	24	
Upper respiratory tract infection			
subjects affected / exposed	44 / 293 (15.02%)	46 / 291 (15.81%)	
occurrences (all)	51	59	
Viral rash			
subjects affected / exposed	17 / 293 (5.80%)	6 / 291 (2.06%)	
occurrences (all)	18	6	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 February 2014	Amendment 1: modified to include the new co-primary immunogenicity objective and hypothesis; added extended safety follow-up period (through Day 271); modified exclusion criteria; increased sample size; included GMTs (including VZV antibody as primary endpoints.
13 May 2014	Amendment 2: modified exclusion criterion.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported