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

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:

Results analysis stage

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

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

Notes:

General information about the trial

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.

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	07 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 611
Worldwide total number of subjects	611
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)	611
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study 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
Arm title	VARIVAX™ New Seed Process + M-M-R II™

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.

Arm title	VARIVAX™ 2007 Process + M-M-R II™

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.

Number of subjects in period 1	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™
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.	

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 >=5 Glycoprotein Enzyme-linked Immunosorbent Assay (gpELISA) Units/mL

End point title	Percentage of Participants With Varicella Zoster Virus (VZV) Antibody Levels >=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 >=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 (>=102.2 °F Oral Equivalent)

End point title	Percentage of Participants With Fever (>=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 (>=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

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

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

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

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

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

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

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

End point timeframe:

Up to 5 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)				
Injection-site erythema	20.6	22.5		
Injection-site swelling	16.2	12		
Injection-site pain/tenderness	22.4	24.3		

Statistical analyses

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

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.

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

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 %

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported