Clinical trial results:
Double blinded, randomized, Priorix®- and placebo-controlled, trial to evaluate the optimal dose of MV-CHIK vaccine (against Chikungunya virus) in regard to immunogenicity, safety and tolerability in healthy volunteers

Summary

EudraCT number	2015-004037-26
Trial protocol	DE AT
Global end of trial date	16 April 2018

Results information

Result version number	v1
This version publication date	09 February 2020
First version publication date	09 February 2020

Trial information

Trial identification

Sponsor protocol code	MV-CHIK-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02861586
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Themis Bioscience GmbH
Sponsor organisation address	Muthgasse 11/2, Vienna, Austria, 1190
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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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2018
Global end of trial reached?	Yes
Global end of trial date	16 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the immunogenicity and safety of MV-CHIK 28 days after primary immunization regime, comprising one or two vaccinations.

Protection of trial subjects:

Subjects' safety was an essential concern in this clinical study MV-CHIK-202 and was addressed in the clinical study protocol:
-Physical examination: During each study visit subjects underwent a symptom-directed physical examination and the assessment of vital signs like systolic and diastolic blood pressure, pulse and body temperature, allowed to detect and record adverse conditions.
-Post vaccination reactogenicity assessment: All subjects were observed for 1 hour after each vaccination in order to investigate local and systemic tolerability and to ensure the subjects wellbeing before discharge.
-AEs: For general safety reasons, all subjects that at least received one vaccination were followed up for at least 28 days after the last vaccination.
-Body temperature: All subjects received a thermometer and were asked to note their daily body temperature in a diary for 7 days after each vaccination to perceive side effects.
-Subject diary: Solicited AEs were recorded by the subjects by checking the presence of listed symptoms in a subject's diary. The diary provided also space for noting unsolicited AEs and concomitant medication. This enabled the subjects to better remember AEs and the investigator to gather and assess AEs in more detail.
-Laboratory parameters: were regularly measured to reveal clinically relevant lab values on hematology, blood chemistry, coagulation parameters and urinalysis. All lab results were evaluated carefully by the investigator to identify adverse conditions.
-Safety stopping rules: An independent DSMB was installed to review safety information, and if necessary, to determine whether study or individual subject stopping rules have been met.
-Data Safety Monitoring Board (DSMB): In close cooperation with the DSMB and the investigators the protection of study participants was assured.

Background therapy:

n.a.

Evidence for comparator:

Priorix® (Glaxo Smith Kline GSK) a measles, mumps, rubella vaccine was used as a control-vaccine because the contained attenuated Schwarz measles virus strain is the same strain, used as backbone in MV-CHIK.

Actual start date of recruitment	17 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 168
Country: Number of subjects enrolled	Germany: 95

Worldwide total number of subjects	263
EEA total number of subjects	263

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	263
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject in, Austria: 17-Aug-2016
Last subjec out, Austria: 11-Jan-2018
First subject in, Germany: 04-May-2017
Last subjec out, Germany: 16-Apr-2018

Pre-assignment

Screening details:

To confirm the health status of volunteers the following data and parameters were assessed during screening:
Medical/vacination history, physical examination, hematology, coagulation parameters, HIV, hepatitis B/C, urinalysis

Period 1

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

Blinding implementation details:

This study was conducted in a double-blind manner in regard to assignment to Treatment Groups A, B, C or D.
An assignment to the measles booster groups M1 and M2 was apparent to both, subject and study personnel, but the vaccination sequence was kept double-blind (allocation to M1 or to M2 was unknown).
Vaccine was prepared by authorized unblinded personnel otherwise not involved in the conduct of the study. Readyly prepared syringes were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Group A

Arm description:

Treatment group A received i.m. vaccinations with MV-CHIK low dose (5x10E4 (± 0.5 log) TCID50 per 0.3 mL) on study day 0 and 28, placebo on day 196.

Arm type	Experimental
Investigational medicinal product name	MV-CHIK low dose 5x10E4 (± 0.5 log) TCID50/dose
Investigational medicinal product code	MV-CHIK
Other name	Chikungunya vaccine
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Treatment group A received i.m. vaccinations with 0.3 ml MV-CHIK low dose on study day 0 and 28, and 0.3 ml placebo on day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	Physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Treatment group A received i.m. vaccinations with 0.3 ml MV-CHIK low dose on study day 0 and 28, and 0.3 ml placebo on day 196.

Arm title	Treatment Group B

Arm description:

Group B subjects received i.m. vaccinations with placebo on study day 0; MV-CHIK low dose (5x10E4 (± 0.5 log) TCID50 per 0.3 mL) on day 28 and MV-CHIK boosting dose on day 196.

Arm type	Experimental
Investigational medicinal product name	MV-CHIK low dose 5x10E4 (± 0.5 log) TCID50/ dose
Investigational medicinal product code	MV-CHIK
Other name	Chikungunya vaccine
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Group B subjects received i.m. vaccinations with 0.3 ml placebo on study day 0, and 0.3 ml MV-CHIK low dose on day 28 and on day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Group B subjects received i.m. vaccinations with 0.3 ml placebo on study day 0, and 0.3 ml MV-CHIK low dose on day 28 and on day 196.

Arm title	Treatment Group C

Arm description:

Group C received i.m. vaccinations with MV-CHIK high dose (5x10E5 (± 0.5 log) TCID50 per 0.3 mL) on study day 0 and 28, placebo on day 196.

Arm type	Experimental
Investigational medicinal product name	MV-CHIK high dose 5x10E5 (± 0.5 log) TCID50/ dose
Investigational medicinal product code	MV-CHIK
Other name	Chikungunya vaccine
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intranasal use

Dosage and administration details:

Group C received i.m. vaccinations with 0.3 ml MV-CHIK high dose on study day 0 and 28, and 0.3 ml placebo on day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	Physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Group C received i.m. vaccinations with 0.3 ml MV-CHIK high dose on study day 0 and 28, and 0.3 ml placebo on day 196.

Arm title	Treatment Group D

Arm description:

Group D received i.m. vaccinations with placebo on study day 0, MV-CHIK high dose (5x10E5 (± 0.5 log) TCID50 per 0.3 mL) on study day 28 and MV-CHIK
boosting dose on day 196.

Arm type	Experimental
Investigational medicinal product name	MV-CHIK high dose 5x10E5 (± 0.5 log) TCID50/ dose
Investigational medicinal product code	MV-CHIK
Other name	Chikungunya vaccine
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intranasal use

Dosage and administration details:

Group D received i.m. vaccinations with 0.3 ml placebo on study day 0, and 0.3 ml MV-CHIK high dose

on study day 28 and on day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	Physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Group D received i.m. vaccinations with 0.3 ml placebo on study day 0, and 0.3 ml MV-CHIK high dose on study day 28 and on day 196.

Arm title	Treatment Group M1

Arm description:

Measles Booster Group 1, M1: received i.m. vaccinations with Priorix® 28 days prior to vaccination with MV-CHIK on day 0 and 28, and placebo on day 168 and 196.

Arm type	Experimental
Investigational medicinal product name	Priorix® measles, mumps rubella vaccine
Investigational medicinal product code	Priorix® controll vaccine
Other name	comperator
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects of group M1 received the control vaccine (Priorix®) 28 days prior to two MV-CHIK vaccinations on day 0 and 28, followed by two placebo injections on day 168 and 196.

Arm title	Treatment Group M2

Arm description:

Measles Booster Group 2, M2: received i.m. vaccinations with Priorix® 28 days prior to placebo on day 0 and 28, and MV-CHIK on day 168 and 196.

Arm type	Experimental
Investigational medicinal product name	Priorix® measles, mumps, rubella vaccine
Investigational medicinal product code	Priorix®controll vaccine
Other name	comperator
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Group M2 received the control vaccine (Priorix®) 28 days prior to two placebo injections on day 0 and 28, followed by two MV-CHIK vaccinations on day 168 and 196.

Arm title	Control Group CV1, A/C

Arm description:

Control Group CV1, A/C received i.m. vaccinations with Priorix® on study day 0 and 28, and placebo on day 196.

Arm type	Active comparator
Investigational medicinal product name	Priorix® measles, mumps, rubella vaccine
Investigational medicinal product code	Priorix® control vaccine
Other name	comperator
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Control Group CV1, A/C received i.m. vaccinations with Priorix® on study day 0 and 28, and placebo on day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	Physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Control Group CV1, A/C received i.m. vaccinations with Priorix® on study day 0 and 28, and placebo on day 196.

Arm title	Control Group CV2, B/D

Arm description:

Control Group CV2, B/D received i.m. vaccinations with placebo on study day 0, Priorix® on day 28 and one boosting dose with Priorix® on day 196.

Arm type	Active comparator
Investigational medicinal product name	Priorix® measles, mumps, rubella vaccine
Investigational medicinal product code	Priorix® control vaccine
Other name	comperator
Pharmaceutical forms	Powder and solvent for solution for injection/skin-prick test
Routes of administration	Intramuscular use

Dosage and administration details:

Control Group CV2, B/D received i.m. vaccinations with placebo on study day 0, and Priorix® on day 28 and day 196.

Investigational medicinal product name	Placebo NaCl 0.9%
Investigational medicinal product code	Placebo
Other name	Physiological saline solution
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Control Group CV2, B/D received i.m. vaccinations with placebo on study day 0, and Priorix® on day 28 and day 196.

Number of subjects in period 1	Treatment Group A	Treatment Group B	Treatment Group C
Started	51	47	47
Completed	49	44	47
Not completed	2	3	0
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	1	1	-

Number of subjects in period 1	Treatment Group D	Treatment Group M1	Treatment Group M2
Started	50	18	16
Completed	44	16	15
Not completed	6	2	1
Consent withdrawn by subject	2	1	-
Adverse event, non-fatal	1	-	-
Lost to follow-up	3	1	1

Number of subjects in period 1	Control Group CV1, A/C	Control Group CV2, B/D
Started	18	16

Completed	16	16
Not completed	2	0
Consent withdrawn by subject	-	-
Adverse event, non-fatal	-	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	263	263	
Age categorical			
study population: healthy male and female voluntees aged 18 -55 years			
Units: Subjects			
18-55	263	263	
Gender categorical Units: Subjects			
Female	140	140	
Male	123	123	

End points

End points reporting groups

Reporting group title	Treatment Group A

Reporting group description:

Treatment group A received i.m. vaccinations with MV-CHIK low dose (5x10E4 (± 0.5 log) TCID50 per 0.3 mL) on study day 0 and 28, placebo on day 196.

Reporting group title	Treatment Group B

Reporting group description:

Group B subjects received i.m. vaccinations with placebo on study day 0; MV-CHIK low dose (5x10E4 (± 0.5 log) TCID50 per 0.3 mL) on day 28 and MV-CHIK boosting dose on day 196.

Reporting group title	Treatment Group C

Reporting group description:

Group C received i.m. vaccinations with MV-CHIK high dose (5x10E5 (± 0.5 log) TCID50 per 0.3 mL) on study day 0 and 28, placebo on day 196.

Reporting group title	Treatment Group D

Reporting group description:

Group D received i.m. vaccinations with placebo on study day 0, MV-CHIK high dose (5x10E5 (± 0.5 log) TCID50 per 0.3 mL) on study day 28 and MV-CHIK
boosting dose on day 196.

Reporting group title	Treatment Group M1

Reporting group description:

Measles Booster Group 1, M1: received i.m. vaccinations with Priorix® 28 days prior to vaccination with MV-CHIK on day 0 and 28, and placebo on day 168 and 196.

Reporting group title	Treatment Group M2

Reporting group description:

Measles Booster Group 2, M2: received i.m. vaccinations with Priorix® 28 days prior to placebo on day 0 and 28, and MV-CHIK on day 168 and 196.

Reporting group title	Control Group CV1, A/C

Reporting group description:

Control Group CV1, A/C received i.m. vaccinations with Priorix® on study day 0 and 28, and placebo on day 196.

Reporting group title	Control Group CV2, B/D

Reporting group description:

Control Group CV2, B/D received i.m. vaccinations with placebo on study day 0, Priorix® on day 28 and one boosting dose with Priorix® on day 196.

Subject analysis set title	Modified Intent-to-Treat Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The exploratory immunogenicity analyses were based on the modified Intent-to-treat (mITT) population. The mITT population included all randomized subjects who received at least one vaccination. Subjects were analyzed according to the treatment group they were randomized to, rather than by the actual treatment they received.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) population was defined as the mITT population minus subjects with at least one major protocol deviation. The PP population excluded an enrolled subject if one of the following criteria was met:
 Immunosuppressive drugs: Use of corticosteroids (excluding topical preparations) or immunosuppressive drugs within 30 days prior to vaccination, or anticipated use during the trial
 Subjects with any confirmed immunosuppressive or immunodeficient condition, including HIV, hepatitis A, B or C infection or a family history of congenital or hereditary immunodeficiency
 Subjects who received the wrong or no study medication
 Subjects with other major protocol deviations

Primary: Immunogenicity on day 56 by PRNT50	
End point title	Immunogenicity on day 56 by PRNT50
End point description:	
Immunogenicity on study day 56 confirmed by the presence of functional anti-chikungunya antibodies as determined by the plaque reduction neutralization test (PRNT50)	
End point type	Primary
End point timeframe:	
Functional anti-chikungunya antibodies measured by the plaque reduction neutralization test (PRNT50) on study day 56	

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	44	47	44
Units: Titer				
geometric mean (standard deviation)	50.2 (± 127.69)	12.9 (± 100.47)	174.8 (± 436.11)	33.6 (± 59.38)

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	16	16
Units: Titer				
geometric mean (standard deviation)	80.0 (± 233.80)	5.0 (± 0.00)	5.0 (± 0.00)	5.0 (± 0.00)

Statistical analyses

Statistical analysis title	ANOVA PRNT50 at Day 56
Statistical analysis description:	
ANOVA with fixed factor treatment group for GMT of functional antibodies by PRNT50 at day 56.	
Comparison groups	Treatment Group A v Treatment Group B v Treatment Group C v Treatment Group D v Treatment Group M1 v Treatment Group M2 v Control Group CV1, A/C v Control Group CV2, B/D
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Anti-measles antibodies by ELISA

End point title	Anti-measles antibodies by ELISA

End point description:

Measurement of anti-measles antibody titers on day 0, 28, and 56 and additionally for group M1 and M2 on day -28 as determined by ELISA. Please note that for some timepoints testing has not been done. "Not done" cannot be entered but only numerical values. "9999" should serve as indicator of a test which was not performed.

End point type	Secondary

End point timeframe:

Anti-measles antibodies on day 0, 28, and 56 and additionally for group M1 and M2 on day -28 as determined by ELISA

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	44	47	44
Units: Titer				
geometric mean (standard deviation)				
Day -28	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 0	456.2 (± 1398.54)	398.1 (± 1267.55)	495.0 (± 1181.36)	401.8 (± 1073.54)
Day 28	1509.4 (± 1360.83)	396.9 (± 1183.04)	2343.9 (± 1357.29)	2343.9 (± 1357.29)
Day 56	1651.8 (± 1384.39)	1255.0 (± 1279.28)	2750.5 (± 1284.23)	2750.5 (± 1284.23)

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	16	16
Units: Titer				
geometric mean (standard deviation)				
Day -28	542.6 (± 1118.52)	304.5 (± 343.53)	9999 (± 9999)	9999 (± 9999)
Day 0	785.6 (± 1149.47)	645.9 (± 850.56)	693.9 (± 1307.42)	390.4 (± 1106.86)
Day 28	1761.5 (± 1578.85)	561.2 (± 385.36)	1200.6 (± 1129.77)	447.5 (± 1139.37)
Day 56	1825.2 (± 1459.93)	521.4 (± 455.37)	1129.4 (± 1168.63)	673.8 (± 917.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Shedding (Urine)

End point title	Shedding (Urine)[1]

End point description:

Shedding of live recombinant virus until day 196 (in a subset of subjects at one site)

End point type	Secondary

End point timeframe:

Shedding of live recombinant virus on day 0, 7, 10, 14, 28 and day 196 after the first injection

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistic calculations were planned or performed - not one case of sheeding was observed.

Shedding analysis relies on PCR methods amplifying measles sequences. As M1 and M2 groups receive a measles vaccination and the study vaccination (modified measles virus), a potential positive result would not be indicative of the reason and therefore these groups were not tested for shedding.

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	8	4
Units: Subjects shedding measles virus				
Day 0	0	0	0	0
Day 7	0	0	0	0
Day 10	0	0	0	0
Day 14	0	0	0	0
Day 28	0	0	0	0
Day 196	0	0	0	0

End point values	Control Group CV1, A/C	Control Group CV2, B/D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: Subjects shedding measles virus				
Day 0	0	0		
Day 7	0	0		
Day 10	0	0		
Day 14	0	0		
Day 28	0	0		
Day 196	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity on days 0, 28, 196, and 224 (and 168 for M1 and M2) by PRNT50

End point title	Immunogenicity on days 0, 28, 196, and 224 (and 168 for M1

	and M2) by PRNT50

End point description:

Immunogenicity on days 0, 28, 196 and 224; additionally, for group M1 and M2 on day 168 as confirmed by the presence of functional anti-chikungunya antibodies as determined by the plaque reduction neutralization test (PRNT50) and by ELISA.
- please note that in the protocol the timepoint "day -28" for M1 and M2 groups is also mentioned; however that timepoint was used for testing pre-existing measles titer but has no additional value for the chikungunya-PRNTs as it would be only an additional pre-vaccination value. Please note that for some timepoints testing has not been done. "Not done" cannot be entered but only numerical values. "9999" should serve as indicator of a test which was not performed.

End point type	Secondary

End point timeframe:

Study day 0 to day 224

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	44	47	44
Units: Titer				
geometric mean (standard deviation)				
Day 0	5.1 (± 0.71)	5.3 (± 3.16)	5.0 (± 0.00)	5.0 (± 0.00)
Day 28	63.4 (± 10.0)	5.5 (± 3.82)	25.7 (± 52.22)	5.1 (± 0.75)
Day 168	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)	9999 (± 9999)
Day 196	13.5 (± 33.46)	6.4 (± 8.29)	38.8 (± 70.59)	24.1 (± 106.25)
Day 224	14.6 (± 37.87)	70.5 (± 174.57)	41.8 (± 105.55)	609.8 (± 949.70)

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	16	16
Units: Titer				
geometric mean (standard deviation)				
Day 0	5.0 (± 0.00)	5.0 (± 0.00)	5.0 (± 0.00)	5.0 (± 0.00)
Day 28	13.5 (± 40.52)	5.0 (± 0.00)	5.0 (± 0.00)	5.0 (± 0.00)
Day 168	28.9 (± 52.25)	5.0 (± 0.00)	9999 (± 9999)	9999 (± 9999)
Day 196	24.1 (± 106.25)	11.5 (± 26.04)	5.0 (± 0.00)	5.0 (± 0.00)
Day 224	18.3 (± 87.50)	66.5 (± 172.62)	5.0 (± 0.00)	5.0 (± 0.00)

Statistical analyses

Statistical analysis title	ANOVA to compare PRNT titers

Statistical analysis description:

An ANOVA with the fixed factors treatment group (CV1, CV2, A, B, C, D, M1, M2) will be used to compare PRNT functional antibody geometric mean titers (GMT) per visit.

Comparison groups	Treatment Group A v Treatment Group B v Treatment Group C v Treatment Group D v Treatment Group M1 v Treatment Group M2 v Control Group CV1, A/C v Control Group CV2, B/D
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Shedding (Saliva)

End point title	Shedding (Saliva)[2]

End point description:

Shedding of live recombinant virus until day 196 (in a subset of subjects at one site)

End point type	Secondary

End point timeframe:

Shedding of live recombinant virus on day 0, 7, 10, 14, 28 and day 196 after the first injection

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No statistic calculations were planned or performed - not one case of sheeding was observed.

Shedding analysis relies on PCR methods amplifying measles sequences. As M1 and M2 groups receive a measles vaccination and the study vaccination (modified measles virus), a potential positive result would not be indicative of the reason and therefore these groups were not tested for shedding.

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	8	4
Units: Subjects shedding measles virus				
Day 0	0	0	0	0
Day 7	0	0	0	0
Day 10	0	0	0	0
Day 14	0	0	0	0
Day 28	0	0	0	0
Day 196	0	0	0	0

End point values	Control Group CV1, A/C	Control Group CV2, B/D		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: Subjects shedding measles virus				
Day 0	0	0		
Day 7	0	0		

Day 10	0	0		
Day 14	0	0		
Day 28	0	0		
Day 196	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Solicited Adverse Events (Safety population)

End point title	Solicited Adverse Events (Safety population)

End point description:

Number of observed AEs per treatment group.

End point type	Secondary

End point timeframe:

Throughout the study participation

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	47	47	50
Units: Observations				
Numer of observations	35	32	37	41

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	18	16
Units: Observations				
Numer of observations	13	10	14	10

Statistical analyses

Statistical analysis title	Fisher exact test to compare AE rates
Comparison groups	Treatment Group A v Treatment Group B v Treatment Group C v Treatment Group D v Treatment Group M1 v Treatment Group M2 v Control Group CV1, A/C v Control Group CV2, B/D

Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	≤ 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Notes:

[3] - Pairwise comparison of treatment groups.

Secondary: Treatment Emergent Adverse Events

End point title	Treatment Emergent Adverse Events

End point description:

Observations of unsolicited treatment emergent adverse events (TEAEs).

End point type	Secondary

End point timeframe:

Throughout the study.

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	47	47	50
Units: Observations				
TEAEs	29	27	22	18
Serious TEAEs	1	2	0	1
Severe TEAEs	1	2	0	2
Related TEAEs	8	11	4	10
Medically Attended TEAEs	12	15	9	8
TEAEs where an action was taken	0	1	0	1
TEAEs of special interest	2	2	0	1

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	18	16
Units: Observations				
TEAEs	11	9	10	7
Serious TEAEs	0	0	1	1
Severe TEAEs	1	1	1	0
Related TEAEs	4	5	2	1
Medically Attended TEAEs	4	3	3	1
TEAEs where an action was taken	0	0	0	1
TEAEs of special interest	2	0	0	0

Statistical analyses

Statistical analysis title	Fisher exact test to compare AE rates
Statistical analysis description:	
Pairwise comparison of TEAEs between treatment groups.	
Comparison groups	Treatment Group A v Treatment Group B v Treatment Group C v Treatment Group D v Treatment Group M1 v Treatment Group M2 v Control Group CV1, A/C v Control Group CV2, B/D
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Induction of a Chikungunya virus specific T cell response (subset of subjects)

End point title	Induction of a Chikungunya virus specific T cell response (subset of subjects)
End point description:	
Please note that for some timepoints testing has not been done. "Not done" cannot be entered but only numerical values. "9999" should serve as indicator of a test which was not performed.	
End point type	Secondary
End point timeframe:	
Study Days 0, 28, 56, and 224	

End point values	Treatment Group A	Treatment Group B	Treatment Group C	Treatment Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	12	14	11
Units: Subjects with CHIKV-specific T-cells				
Day 0	0	1	0	0
Day 28	2	9999	1	9999
Day 56	6	3	7	1
Day 224	5	4	3	3

End point values	Treatment Group M1	Treatment Group M2	Control Group CV1, A/C	Control Group CV2, B/D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	4	5	5
Units: Subjects with CHIKV-specific T-cells				
Day 0	0	9999	0	0
Day 28	9999	9999	0	9999
Day 56	3	0	0	1
Day 224	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 0 after the first vaccination up to day 224	
Adverse event reporting additional description:	
Solicited and unsolicited local and systemic adverse events (AEs) were recorded throughout the study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Treatment Group A
Reporting group description:	
Group A subjects received vaccinations with MVCHIK low dose on study day 0 and 28, placebo on day 196.	
Reporting group title	Treatment Group B
Reporting group description:	
Group B subjects received vaccinations with placebo on study day 0. MV-CHIK low dose on day 28 and MV-CHIK boosting dose on day 196.	
Reporting group title	Treatment Group C
Reporting group description:	
Group C subjects received vaccinations with MVCHIK high dose on study day 0 and 28, placebo on day 196.	
Reporting group title	Treatment Group D
Reporting group description:	
Group D subjects received vaccinations with placebo on study day 0, MV-CHIK high dose on study day 28 and MV-CHIK boosting dose on day 196.	
Reporting group title	Treatment Group M1
Reporting group description:	
Measles Booster Group M1 subjects received vaccinations with Priorix® on study day -28, MV-CHIK on day 0 and 28 and placebo on day 168 and 196.	
Reporting group title	Treatment Group M2
Reporting group description:	
Measles Booster Group M2 subjects received vaccinations with Priorix® on study day -28, placebo on day 0 and 28 and MV-CHIK on day 168 and 196.	
Reporting group title	Control Group CV1, A/C
Reporting group description:	
Control Group CV1, A/C subjects received vaccinations with Priorix® on study day 0 and 28, placebo on day 196.	
Reporting group title	Control Group CV2, B/D
Reporting group description:	
Control Group CV2, B/D subjects received vaccinations with placebo on study day 0, Priorix® on day 28 and one boosting dose with Priorix® on day 196.	

Serious adverse events	Treatment Group A	Treatment Group B	Treatment Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 51 (1.96%)	2 / 47 (4.26%)	0 / 47 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer	Additional description: One subject of control group CV1 experienced laryngeal cancer 5 days after receiving placebo. The subject was hospitalized and biopsy and tracheotomy were performed. The event was assessed severe in intensity and considered not related.		
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer	Additional description: One subject of group D experienced papillary thyroid cancer 4 months after receiving the first dose of MV-CHIK. The event was considered severe in intensity and not related to the study drug. Subject terminated early after Visit 3 due to this SAE.		
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament rupture	Additional description: 1 subject of group B experienced ligament rupture left knee 3 months and 12 days after receiving the first dose of MV-CHIK. The subject was hospitalized and surgery was performed. The event was considered not related to the study drug.		
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion	Additional description: 1 subject group B experienced suspected abortion 1 month and 10 days after receiving placebo. This was considered an important medical event and was judged to be mild and possibly related to the study treatment.		
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Umbilical hernia	Additional description: 1 subject of group A experienced umbilical hernia 4 weeks after the second dose of MVCHIK. The subject was hospitalized and surgery was performed.The event was considered moderate in severity and not related to the study drug.		
subjects affected / exposed	1 / 51 (1.96%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus	Additional description: 1 subject of control group CV2 experienced type 2 diabetes mellitus reported the same month the subject received the first dose of control vaccine. The subject was hospitalized and a diagnostic test performed. The event was assessed not related.		

subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment Group D	Treatment Group M1	Treatment Group M2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 50 (2.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer	Additional description: One subject of control group CV1 experienced laryngeal cancer 5 days after receiving placebo. The subject was hospitalized and biopsy and tracheotomy were performed. The event was assessed severe in intensity and considered not related.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer	Additional description: One subject of group D experienced papillary thyroid cancer 4 months after receiving the first dose of MV-CHIK. The event was considered severe in intensity and not related to the study drug. Subject terminated early after Visit 3 due to this SAE.		
subjects affected / exposed	1 / 50 (2.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament rupture	Additional description: 1 subject of group B experienced ligament rupture left knee 3 months and 12 days after receiving the first dose of MV-CHIK. The subject was hospitalized and surgery was performed. The event was considered not related to the study drug.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion	Additional description: 1 subject group B experienced suspected abortion 1 month and 10 days after receiving placebo. This was considered an important medical event and was judged to be mild and possibly related to the study treatment.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Umbilical hernia	Additional description: 1 subject of group A experienced umbilical hernia 4 weeks after the second dose of MVCHIK. The subject was hospitalized and surgery was performed.The event was considered moderate in severity and not related to the study drug.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus	Additional description: 1 subject of control group CV2 experienced type 2 diabetes mellitus reported the same month the subject received the first dose of control vaccine. The subject was hospitalized and a diagnostic test performed. The event was assessed not related.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control Group CV1, A/C	Control Group CV2, B/D	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer	Additional description: One subject of control group CV1 experienced laryngeal cancer 5 days after receiving placebo. The subject was hospitalized and biopsy and tracheotomy were performed. The event was assessed severe in intensity and considered not related.		
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer	Additional description: One subject of group D experienced papillary thyroid cancer 4 months after receiving the first dose of MV-CHIK. The event was considered severe in intensity and not related to the study drug. Subject terminated early after Visit 3 due to this SAE.		
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament rupture	Additional description: 1 subject of group B experienced ligament rupture left knee 3 months and 12 days after receiving the first dose of MV-CHIK. The subject was hospitalized and surgery was performed. The event was considered not related to the study drug.		
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pregnancy, puerperium and perinatal conditions			
Abortion	Additional description: 1 subject group B experienced suspected abortion 1 month and 10 days after receiving placebo. This was considered an important medical event and was judged to be mild and possibly related to the study treatment.		
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Umbilical hernia	Additional description: 1 subject of group A experienced umbilical hernia 4 weeks after the second dose of MVCHIK. The subject was hospitalized and surgery was performed.The event was considered moderate in severity and not related to the study drug.		
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus	Additional description: 1 subject of control group CV2 experienced type 2 diabetes mellitus reported the same month the subject received the first dose of control vaccine. The subject was hospitalized and a diagnostic test performed. The event was assessed not related.		
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
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	Treatment Group A	Treatment Group B	Treatment Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 51 (82.35%)	39 / 47 (82.98%)	39 / 47 (82.98%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	2	1	0
Axillary pain			

subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 51 (1.96%)	1 / 47 (2.13%)	1 / 47 (2.13%)
occurrences (all)	2	3	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 47 (2.13%)	4 / 47 (8.51%)
occurrences (all)	1	1	5
Cough			
subjects affected / exposed	1 / 51 (1.96%)	2 / 47 (4.26%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Sneezing			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	7 / 51 (13.73%)	2 / 47 (4.26%)	1 / 47 (2.13%)
occurrences (all)	8	2	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 51 (3.92%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eye pruritus			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 51 (5.88%)	0 / 47 (0.00%)	2 / 47 (4.26%)
occurrences (all)	3	0	2
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Toothache			
subjects affected / exposed	1 / 51 (1.96%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			

subjects affected / exposed	1 / 51 (1.96%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Erythema multiforme			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 51 (3.92%)	2 / 47 (4.26%)	2 / 47 (4.26%)
occurrences (all)	2	2	3
Myalgia			
subjects affected / exposed	2 / 51 (3.92%)	2 / 47 (4.26%)	0 / 47 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 51 (13.73%)	4 / 47 (8.51%)	4 / 47 (8.51%)
occurrences (all)	7	4	5
Rhinitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 47 (0.00%)	3 / 47 (6.38%)
occurrences (all)	2	0	3
Upper respiratory tract infection			

subjects affected / exposed	3 / 51 (5.88%)	3 / 47 (6.38%)	1 / 47 (2.13%)
occurrences (all)	3	4	2
Urinary tract infection			
subjects affected / exposed	1 / 51 (1.96%)	1 / 47 (2.13%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
Gingivitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 51 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Treatment Group D	Treatment Group M1	Treatment Group M2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 50 (84.00%)	15 / 18 (83.33%)	14 / 16 (87.50%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	3 / 50 (6.00%)	1 / 18 (5.56%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Fatigue			

subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Axillary pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 50 (2.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 50 (4.00%)	2 / 18 (11.11%)	1 / 16 (6.25%)
occurrences (all)	8	4	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 18 (11.11%)	1 / 16 (6.25%)
occurrences (all)	1	3	1
Cough			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Sneezing			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 50 (2.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Contusion			

subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 50 (8.00%)	1 / 18 (5.56%)	2 / 16 (12.50%)
occurrences (all)	9	1	2
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 50 (2.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1

Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 50 (2.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 50 (2.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Erythema multiforme			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 50 (8.00%)	2 / 18 (11.11%)	1 / 16 (6.25%)
occurrences (all)	5	5	1
Rhinitis			

subjects affected / exposed	2 / 50 (4.00%)	2 / 18 (11.11%)	2 / 16 (12.50%)
occurrences (all)	2	3	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vaginal infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 18 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 50 (0.00%)	1 / 18 (5.56%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Control Group CV1, A/C	Control Group CV2, B/D	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 18 (77.78%)	12 / 16 (75.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			

Influenza like illness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Axillary pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sneezing			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Skin abrasion			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Eye pruritus			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Toothache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Erythema multiforme			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Bursitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	2	3	
Rhinitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gingivitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hordeolum			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vaginal infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2016	Protocol Amendment 1 (substantial, dated 26-Apr-2016) incorporated in Protocol version 1.3 (26-Apr-2016) before the first study submission. The protocol was amended: To precisely define the primary endpoint as immunogenicity on Day 56 for all treatment groups To adapt the study design (by shifting study visits) to enable immunogenicity measurements on Day 56 for all treatment groups To change the definition from three cohorts consisting of two different treatment regimens each, to a more reasonable definition of six treatment groups To define the dates of study visits based on an interval of 28 days and to rename the study days as follows: Screening Visit on Study Day -35; Visit 0 on Study Day -28; Visit 1 on Study Day 0; Visit 2 on Study Day 28; Visit 3 on Study Day 56; Visit 4 on Study Day 168; Visit 5 on Study Day 196; Visit 6 on Study Day 224 To state the study objectives more precisely To include a preliminary data analysis To describe the role of the DSMB To remove the safety assessment by telephone call, 12 months after the first vaccination To clarify that the control-vaccine Priorix® can be exchanged by MMR-Vax-Pro® or equal measles vaccine In addition, to correct typos, include some formal changes and update the list of abbreviations

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported