Clinical trial results:
Immunogenicity and safety study of a third measles mumps rubella (MMR-3) vaccine dose in healthy young adults in The Netherlands

Summary

EudraCT number	2016-001104-36
Trial protocol	NL
Global end of trial date	25 March 2020

Results information

Result version number	v1 (current)
This version publication date	12 July 2023
First version publication date	12 July 2023

Trial information

Trial identification

Sponsor protocol code	IIV-291

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NTR: 5911, ABR: NL57282.094.16

Notes:

Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	PO Box 1, Bilthoven, Netherlands, 3720 BA
Public contact	Clinical Expertise Centre, RIVM, mensgebonden-onderzoek@rivm.nl
Scientific contact	Clinical Expertise Centre, RIVM, mensgebonden-onderzoek@rivm.nl

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	Interim
Date of interim/final analysis	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2020
Global end of trial reached?	Yes
Global end of trial date	25 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of third dose of MMR in young adults 18-25 years of age on the development of mumps-specific serum VN antibody titers (against vaccine- and currently circulating wild-type mumps virus strains (genotype G)) and mumps-specific serum antibody IgG titers (including antibody avidity), 10 days, 4 weeks, 1 year and 3 years following vaccination.

Protection of trial subjects:

Available data on the MMR-3 in young adults does not suggest any elevated frequency or unusual patterns of adverse events compared to the MMR-1 and MMR-2 immunizations given within the routine national immunization program (NIP). Participants who despite the advice become pregnant within 4 weeks after MMR vaccination, will be strongly recommended to consult a physician.
The burden and risk of blood and saliva sampling is considered low. Blood collection could result in a small bruise at the location of injection, which will disappear within a few days. Collection of finger prick blood is regarded an adequate and safe alternative for full venous blood puncture. The applied lancet is easy to use, sterile and with a pricking needle which is designed to prevent exposure and re-use. Risk of infecting someone via the lancet is therefore very unlikely. The method has been successfully applied in a previous RIVM study, “Retrospective assessment of symptomatic and asymptomatic mumps virus infection: assessing attack rates and correlates of protection” (NL38042.041.11).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2016
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	Netherlands: 147
Worldwide total number of subjects	147
EEA total number of subjects	147

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)	147
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place as of September 2016 among students (18-25 years of age), in the surroundings of Haarlem and Amsterdam, The Netherlands. Recruitment was via email, Facebook and flyers. First inclusion 13-10-2016, last inclusion 06-04-2017.

Pre-assignment

Screening details:

During a telephone call, check:
Generally healthy?
For woman: Are you (possibly) pregnant? Do you give breast feeding?
Ever received a third BMR vaccination?
Received two BMR vaccinations as a child (according to the Dutch National Immunization Program)?
Participated in other trials with medication in the past 4 weeks?

Period 1

Period 1 title	MMR-3 immunization (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding

Arms

Arm title	MMR-3 immunization

Arm description: -

Arm type	Experimental
Investigational medicinal product name	M-M-RVAXPRO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains:
Measles virus1 Enders' Edmonston strain (live, attenuated) ……..…..not less than 1x103 TCID50*
Mumps virus1 Jeryl Lynn™ [Level B] strain (live, attenuated)…….…..not less than 12.5x103 TCID50*
Rubella virus2 Wistar RA 27/3 strain (live, attenuated) ……..not less than 1x103 TCID50*

*50% tissue culture infectious dose
1 produced in chick embryo cells.
2 produced in WI-38 human diploid lung fibroblasts.
The vaccine may contain traces of recombinant human albumin (rHA).
This vaccine contains a trace amount of neomycin. See section 4.3 of the SmPC.

Number of subjects in period 1	MMR-3 immunization
Started	147
day 10 after MMR-3 immunization	132
4 weeks following MMR-3 immunization	147
1 year following MMR-3 immunization	134

3 years following MMR-3 immunization	119
Completed	119
Not completed	28
Not participating in the 3 years extension	15
Moved to another region or country	12
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	MMR-3 immunization

Reporting group description: -

Reporting group values	MMR-3 immunization	Total	
Number of subjects	147	147	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	147	147	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	22.4		
full range (min-max)	18 to 25	-	
Gender categorical Units: Subjects			
Female	79	79	
Male	68	68	

End points

End points reporting groups

Reporting group title	MMR-3 immunization
Reporting group description: -	
Subject analysis set title	Pre-MMR-3
Subject analysis set type	Per protocol
Subject analysis set description:	
This trial contains one arm. In order to create multiple arms for the statistical analysis of the primary endpoint, each time point will be defined as one arm.	
Subject analysis set title	10 days post-MMR-3
Subject analysis set type	Per protocol
Subject analysis set description:	
This trial contains one arm. In order to create multiple arms for the statistical analysis of the primary endpoint, each time point will be defined as one arm.	
Subject analysis set title	4 weeks post-MMR-3
Subject analysis set type	Per protocol
Subject analysis set description:	
This trial contains one arm. In order to create multiple arms for the statistical analysis of the primary endpoint, each time point will be defined as one arm.	
Subject analysis set title	1 year post-MMR-3
Subject analysis set type	Per protocol
Subject analysis set description:	
This trial contains one arm. In order to create multiple arms for the statistical analysis of the primary endpoint, each time point will be defined as one arm.	
Subject analysis set title	3 years post-MMR-3
Subject analysis set type	Per protocol
Subject analysis set description:	
This trial contains one arm. In order to create multiple arms for the statistical analysis of the primary endpoint, each time point will be defined as one arm.	

Primary: Anti-mumps, -measles, and -rubella serum antibody levels

End point title	Anti-mumps, -measles, and -rubella serum antibody levels
End point description:	
RU/mL (MuV IgG) IU/mL (MeV IgG, RuV IgG) ND50 (MuV), 50% virus neutralization dose measured against the JL mumps virus vaccine strain as well as against the mumps virus outbreak strain (genotype G).	
End point type	Primary
End point timeframe:	
Baseline, day 0 of MMR-3 immunization Four weeks post MMR-3 immunization (22-36 days) One year post MMR-3 immunization (332-392 days) Three years post MMR-3 immunization (1012-1157 days)	

End point values	Pre-MMR-3	4 weeks post-MMR-3	1 year post-MMR-3	3 years post-MMR-3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	147	147	134	119
Units: RU/mL, ND50, IU/mL, see description				
geometric mean (confidence interval 95%)				
MuV IgG	186 (163 to 211)	306 (273 to 343)	255 (224 to 290)	228 (200 to 259)
ND50 to MuV JL strain	88.8 (72.6 to 109)	119.3 (99.4 to 143)	101.8 (84.6 to 123)	93.8 (76.7 to 115)
ND50 to MuV G strain	65.3 (54.0 to 78.9)	88.4 (74.8 to 104)	82.8 (70.4 to 97.5)	82.8 (67.9 to 101)
MeV IgG	0.69 (0.59 to 0.80)	1.23 (1.10 to 1.38)	1.04 (0.92 to 1.17)	0.87 (0.76 to 1.00)
RuV IgG	36.7 (32.4 to 41.6)	111 (100 to 122)	64.8 (58.1 to 72.5)	49.0 (43.6 to 55.2)

Attachments (see zip file)	Figure 3_35062794/Figure 3_Kaaijk2021_MMR3_3y.pdf

Statistical analyses

Statistical analysis title	MuV IgG pre- versus 4 weeks post-MMR-3

Statistical analysis description:

IgG antibody levels to mumps virus prior to and after a third measles-mumps-rubella vaccine dose. Geometric mean IgG concentrations, with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Observed significant differences were in line with the results of the model fit. Subjects in this analysis = 147, with each 2 time points for comparison.

Comparison groups	Pre-MMR-3 v 4 weeks post-MMR-3
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	MuV FRNT JL strain pre- versus 4 weeks post-MMR-3

Statistical analysis description:

Virus neutralizing antibody levels to mumps virus JL strain prior to and after a third measles-mumps-rubella vaccine dose. ND50 titers, with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Observed significant differences were in line with the results of the model fit. Subjects in this analysis = 147, with each 2 time points for comparison.

Comparison groups	4 weeks post-MMR-3 v Pre-MMR-3

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	MuV FRNT G strain pre- versus 4 weeks post-MMR-3

Statistical analysis description:

Virus neutralizing antibody levels to mumps virus G strain prior to and after a third measles-mumps-rubella vaccine dose. ND50 titers, with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Observed significant differences were in line with the results of the model fit. Subjects in this analysis = 147, with each 2 time points for comparison.

Comparison groups	Pre-MMR-3 v 4 weeks post-MMR-3
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	MeV IgG pre- versus 4 weeks post-MMR-3

Statistical analysis description:

IgG concentrations to measles virus prior to and after a third measles-mumps-rubella vaccine dose. Geometric mean IgG concentrations, with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Observed significant differences were in line with the results of the model fit. Subjects in this analysis = 147, with each 2 time points for comparison.

Comparison groups	Pre-MMR-3 v 4 weeks post-MMR-3
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	RuV IgG pre- versus 4 weeks post-MMR-3

Statistical analysis description:

IgG concentrations to rubella virus prior to and after a third measles-mumps-rubella vaccine dose. Geometric mean IgG concentrations, with 95% confidence interval. Differences in antibody levels between time points were analyzed with two-tailed Wilcoxon matched-pairs signed-rank test. Observed significant differences were in line with the results of the model fit. Subjects in this analysis = 147, with each 2 time points for comparison.

Comparison groups	Pre-MMR-3 v 4 weeks post-MMR-3

Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Adverse Events (AEs) recorded in subjects diaries following receipt of MMR-3

End point title	Adverse Events (AEs) recorded in subjects diaries following receipt of MMR-3

End point description:

MedDRA version 26.0.

Assessed solicited local symptoms were: Vaccination site reaction (= any occurrence of the symptoms), Vaccination site pain, Vaccination site erythema and Vaccination site swelling (all cases were <20 mm). Regardless of intensity grade.
Assessed systemic symptoms were: Post vaccination systemic reaction (= any systemic reaction), Post vaccination fever*, Rash (any rash, not further specified), Salivary gland enlargement, Arthralgia and Myalgia.

*defined as body temperature of 38 degrees Celsius or higher. No cases >39.5 degrees Celsius were reported.

Number of subjects evaluated:
Local symptoms, N=121 Overall, N=71 Female, N=50 Male
Systemic symptoms, N=101 Overall, N=60 Female, N=41 Male

End point type	Secondary

End point timeframe:

Local, AEs recorded d 0-3 after MMR-3 receipt.
Systemic, AEs recorded d 0-28 after MMR-3 receipt.

End point values	MMR-3 immunization			
Subject group type	Reporting group			
Number of subjects analysed	121[1]			
Units: NA				
Vaccination site reaction	21			
Vaccination site pain	15			
Vaccination site erythema	8			
Vaccination site swelling	6			
Post vaccination systemic reaction	33			
Post vaccination fever	4			
Rash	3			
Arthralgia and myalgia	16			
Salivary gland enlargement	18			

Notes:

[1] - "Local: N=121 Overall, N=71 Female, N=50 Male
Systemic: N=101 Overall, N=60 Female, N=41 Male"

Attachments (see zip file)	Local and systemic reaction by gender/jiz188_table_1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-mumps serum antibody levels, 10 days post MMR-3

End point title	Anti-mumps serum antibody levels, 10 days post MMR-3

End point description:

Serum from fingerprick blood. The amount of serum was low. GMC's were not measured, FRNT to MuV JL strain was measured and remaining serum was used for FRNT to MuV G strain.

End point type	Secondary

End point timeframe:

Ten days post MMR-3 immunization (9-15 days days)

End point values	MMR-3 immunization			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: ND50				
geometric mean (confidence interval 95%)				
FRNT to MuV JL strain, 10d post-MMR-3, (N=123)	132.6 (107.1 to 164.1)			
FRNT to MuV G strain, 10d post-MMR-3, (N=73)	90.76 (67.35 to 122.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and SUSARs < 4 weeks after immunization.
AEs occurring directly after immunization (up until day 14).
Local and systemic reactions recorded in the diary day 0-14.

Adverse event reporting additional description:

There were no SAEs and SUSARs. Elective hospital admissions were excluded from SAE reporting.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	MMR-3 immunization

Reporting group description:

AE's were recorded of N=147 participants when spontaneously reported to the study team. The diary entries were not complete. N=121, D1-4 complete (local reactions). N=101, D1-14 complete (systemic reactions).

Serious adverse events	MMR-3 immunization		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 147 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	MMR-3 immunization		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 147 (40.14%)		
Injury, poisoning and procedural complications			
Post vaccination fever			
subjects affected / exposed	4 / 147 (2.72%)		
occurrences (all)	4		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	6 / 147 (4.08%)		
occurrences (all)	6		

Vaccination site erythema subjects affected / exposed occurrences (all) Vaccination site haematoma subjects affected / exposed occurrences (all) Vaccination site pain subjects affected / exposed occurrences (all) Vaccination site swelling subjects affected / exposed occurrences (all) Vessel puncture site haematoma subjects affected / exposed occurrences (all)	8 / 147 (5.44%) 8 6 / 147 (4.08%) 6 15 / 147 (10.20%) 15 6 / 147 (4.08%) 6 5 / 147 (3.40%) 5		
Gastrointestinal disorders Salivary gland enlargement subjects affected / exposed occurrences (all)	18 / 147 (12.24%) 18		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 147 (2.04%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	5 / 147 (3.40%) 5 16 / 147 (10.88%) 16		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2019	Extension of the follow-up period from 1 year to 3 years after vaccination. An extra blood sample (by fingerprick) will be taken 3 years after MMR-3 vaccine receipt, to provide information on the duration of protection to mumps virus infection following vaccination.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No results:
Mumps, Measles and Rubella IgG antibody concentrations and avidity measured at day 10 following MMR-3 (not enough serum in the fingerprick samples).
Mumps IgG and IgA antibody concentrations in saliva (too low/undetectable).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31112277

http://www.ncbi.nlm.nih.gov/pubmed/33269296

http://www.ncbi.nlm.nih.gov/pubmed/34211021

http://www.ncbi.nlm.nih.gov/pubmed/35062794