12 December 2019
EMA/25228/2020
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

M-M-RVAXPRO

measles, mumps and rubella vaccine (live)

Procedure no: EMEA/H/C/000604/P46/038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 20 September 2019, the MAH submitted data from a completed paediatric study for VARIVAX, administered concomitantly with M-M-RVAXPRO, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The results from this single Phase 3 clinical study complement the analytical comparability data of a new manufacturing passage extension (PE34) for VARIVAX.

2.2. Information on the pharmaceutical formulation used in the study

VARIVAX is a live, attenuated vaccine manufactured by Merck & Co., Inc., West Point, PA, US for the prevention of varicella (chickenpox). In this clinical overview, the term "varicella vaccine" is synonymous with varicella virus vaccine live (Oka/Merck).

M-M-RVAXPRO is a live, attenuated vaccine manufactured by Merck & Co., Inc., West Point, PA, US for prevention of measles, mumps, and rubella. In this clinical overview, the term "M-M-R vaccine" is synonymous with measles, mumps, and rubella virus vaccine live, Merck.

Study Vaccine	Unit Dose and Frequency	Route of Administration
VARIVAX PE34 process (Group 1)	0.5 mL after reconstitution 2 doses; 3 months between each dose	Subcutaneous injection
VARIVAX (2016 CP) (Group 2)	0.5 mL after reconstitution 2 doses; 3 months between each dose	Subcutaneous injection
M-M-R II (Groups 1 and 2)	0.5 mL after reconstitution 2 doses; 3 months between each dose	Subcutaneous injection

2.3. Clinical aspects

No changes to the current or targeted indications for either vaccine are being requested. V210-A03 revealed no new information regarding the immunogenicity and safety profile of VARIVAX or the safety profile of M-M-RVAXPRO (for which immunogenicity was not evaluated in this study) and no modifications to the EU product information (SmPC, package leaflet, or texts of outer or immediate packaging) are needed.

2.3.1. Introduction

The MAH submitted a final report for:

- V210 (VARIVAX); A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX Passage Extension 34 (PE34) Process Administered Concomitantly with M-M-R II

2.3.2. Clinical study

Clinical study number and title

V210 (VARIVAX); A Phase 3, Double-Blind, Randomized, Multicenter, Controlled Study to Evaluate the Immunogenicity, Safety, and Tolerability of VARIVAX Passage Extension 34 (PE34) Process Administered Concomitantly with M-M-R II

Description

V210-A03 was a randomized, comparator-controlled, multicenter, double-blind study to evaluate the safety, tolerability, and immunogenicity of the VARIVAX 'PE34 process' vaccine compared with the VARIVAX 2016 commercial product in healthy children 12 to 23 months of age. Both study vaccines were administered concomitantly with M-M-R II (measles, mumps, and rubella vaccine live; V205C, MSD), which is currently licensed as M-MRVAXPRO in the EU and hereafter referred to using the US licensed name of M-M-R II (in text) or M-M-R II (in tables).

Both groups received the same M-M-R II vaccine (the current commercial product).

Indication

VARIVAX

VARIVAX is indicated for vaccination against varicella in individuals from 12 months of age.

VARIVAX can be administered to infants from 9 months of age under special circumstances, such as to conform with national vaccination schedules or in outbreak situations.

VARIVAX may also be administered to susceptible individuals who have been exposed to varicella. Vaccination within 3 days of exposure may prevent a clinically apparent infection or modify the course of the infection. In addition, there are limited data that indicate that vaccination up to 5 days after exposure may modify the course of the infection.

M-M-RVAXPRO

M-M-RVAXPRO is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals from 12 months of age.

M-M-RVAXPRO can be administered to infants from 9 months of age under special circumstances.

For use in measles outbreaks, or for post-exposure vaccination, or, for use in previously unvaccinated individuals older than 9 months who are in contact with susceptible pregnant women, and persons likely to be susceptible to mumps and rubella, see the SmPC.

VARIVAX Manufacturing Process Development

VARIVAX is a preparation of the Oka/Merck strain of live, attenuated VZV. The virus was initially obtained from a child with naturally acquired varicella, then introduced into human embryonic lung cell cultures, and finally propagated in human diploid cell cultures (WI-38).

Further passage of the virus for varicella vaccine was performed at MRL in human diploid cell cultures (MRC-5) that were free of adventitious agents. This live, attenuated varicella vaccine is a sterile, preservative-free, lyophilized preparation for subcutaneous injection.

Each 0.5-mL dose contains a minimum of 1350 PFU of the Oka/Merck strain of VZV. Licensed formulations contain sucrose, phosphate, glutamate, and processed gelatin, with or without urea, as stabilizers.

Manufacturing campaigns of varicella vaccine have been conducted at MSD, all using generally similar manufacturing techniques except for minor modifications. The 1982 to 1983 campaigns were conducted in small-scale research facilities. More recent campaigns were conducted in commercial-scale vaccine production facilities.

In 1997, a number of improvements were made to the manufacturing process in order to increase the yield of vaccine virus. Varicella vaccine manufactured with these process changes is referred to as PUVV. Production Lots of PUVV were first manufactured in 1998.

PUVV is formulated with a PGS stabilizer.

In 1999, PUVV with PGS was reformulated by adding 1.0% urea as an additional stabilizer. The addition of 1.0% urea, combined with an increase in the minimum release potency, supported a minimum end-expiry potency of 1350 PFU/0.5-mL dose when the vaccine is stored for 24 months at 2°C to 8°C. This reformulated, refrigerator-stable, varicella vaccine is referred to as PUVV with PGSU. PUVV with PGSU is the formulation of VARIVAX currently licensed in multiple countries in North and South America, Europe, Oceania, and Asia.

In an effort to extend the lifespan of the existing vaccine master seed, the vaccine passage level was increased from Passage 31 to Passage 32 (P31 PUVV to P32 PUVV), and a new seed process was implemented with VARIVAX NSP. This was one of a series of changes made to ensure that Merck's varicella seed system was sufficient to meet future demands.

In 2017, in an effort to further extend the lifespan of the existing vaccine master seed, the vaccine passage level was increased from the currently approved Passage 32 to the proposed Passage 34 (P32 PUVV to P34 PUVV). The P32 stock seed is then the process input to the drug substance manufacturing process to manufacture the drug substance at P34.

There are no proposed changes to the co-settling stock seed manufacturing process, drug substance manufacturing process, or drug product manufacturing process to implement this extension to P34..

In an effort to complement the available analytical comparability data, the V210-A03 study was designed to assess the immunogenicity, safety, and tolerability of VARIVAX at the proposed passage level of P34 in comparison with VARIVAX at the currently approved passage level of P32 (used in the 2016 CP) when administered concomitantly with M-M-R II (measles, mumps, and rubella virus vaccine live) in healthy children between 12 to 23 months of age.

These changes were instituted as a means to conserve MSD's supply of VZV master seed.

Methods

Objectives

Primary Objective(s) & Hypothesis(es)

1) Objective: To demonstrate that a single dose of VARIVAX PE34 process induces VZV antibody responses 6 weeks Postvaccination 1 that are noninferior to those induced by VARIVAX (2016 CP).

The primary endpoints for measuring the VZV antibody responses were the response rate and the GMT. The response rate was defined as the proportion of participants with VZV antibody titer ≥5 gpELISA units/mL 6 weeks Postvaccination 1 among participants who were seronegative to VZV (titers <1.25 gpELISA units/mL) at baseline.

Hypotheses:

(1) Six weeks Postvaccination 1, VARIVAX PE34 process induces VZV antibody responses that are noninferior to those induced by VARIVAX (2016 CP), as measured by the response rate.

The statistical criterion for noninferiority of the response rate corresponds to the lower bound of the 2-sided 95% CI on the difference in response rates (VARIVAX PE34 process minus VARIVAX [2016 CP]) excluding a decrease of 10 percentage points or more.

(2) Six weeks Postvaccination 1, VARIVAX PE34 process induces VZV antibody responses that are noninferior to those induced by VARIVAX (2016 CP), as measured by the GMT.

The statistical criterion for noninferiority of the GMT corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio (VARIVAX PE34 process/VARIVAX [2016 CP]) being >0.67.

2) Objective: To demonstrate that a single dose of VARIVAX PE34 process induces an acceptable VZV antibody response 6 weeks Postvaccination 1.

Hypothesis:

(3) Six weeks Postvaccination 1, VARIVAX PE34 process induces an acceptable VZV antibody response, as measured by the response rate.

The statistical criterion for an acceptable antibody response corresponds to the lower bound of the 95% CI for the response rate to VZV in the group receiving VARIVAX PE34 process being >76.0%.

Secondary Objective(s) & Hypothesis(es)

3) Objective: To assess the safety and tolerability of the first and second doses of VARIVAX PE34 process.

4) Objective: To summarize the VZV antibody responses after a single dose of VARIVAX PE34 process and after a single dose of VARIVAX (2016 CP). The VZV immunogenicity data were summarized for the antibody response rates, seroconversion rates and GMTs, along with the associated 95% CI for these parameters. No formal testing was conducted.

Success for the study required fulfilling the criteria stated in the 3 hypotheses based on the 2 primary objectives.

Study design

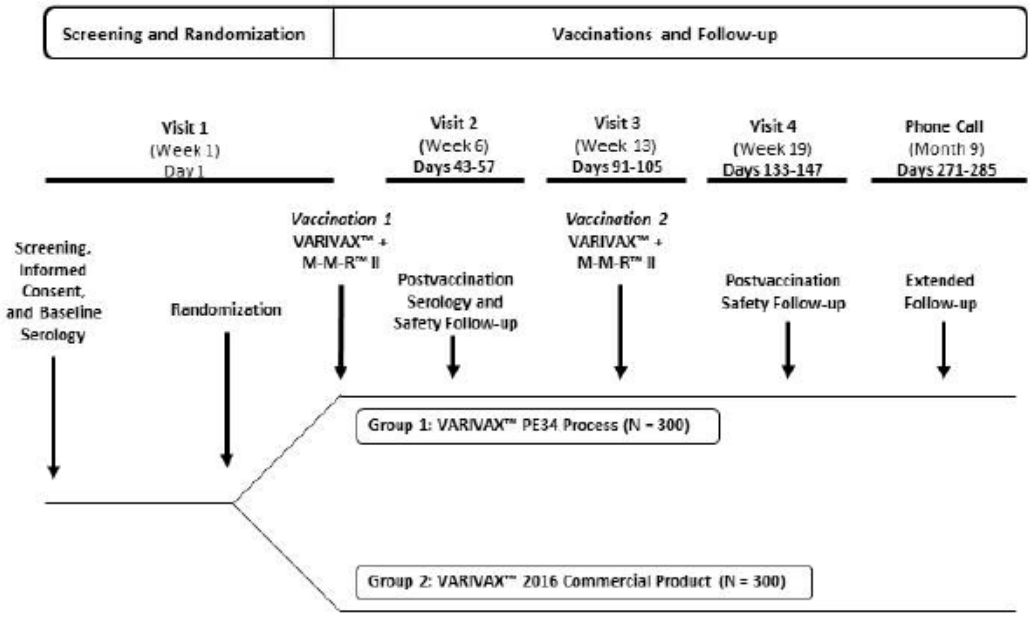
This was a randomized, comparator-controlled, multicenter, double-blind study to evaluate the safety, tolerability, and immunogenicity of the VARIVAX PE34 process compared with the VARIVAX (2016 CP) in healthy children 12 to 23 months of age.

Approximately 600 participants were planned for enrolment. Participants were randomized into 1 of 2 vaccination groups (ratio 1:1) with approximately 300 participants per group.

Group 1 received 2 doses of VARIVAX PE34 process, given concomitantly with M-M-R II, approximately 3 months apart. Group 2 received 2 doses of VARIVAX (2016 CP), given concomitantly with M-M-R II, approximately 3 months apart.

The enrolment period for the study was expected to be approximately 9 months. Once enrolled, the total duration of the study for a participant (from first visit to last contact) was approximately 9 months. A participant was considered to have completed the study when (1) both scheduled study vaccinations were received, (2) both blood samples had been collected, and (3) the 42-day safety data after each study vaccination had been collected. A participant was considered to have completed the extended safety follow-up when the last protocol-specified phone call was completed and all safety data had been collected.

Study Diagram



Study population /Sample size

A total of 600 healthy participants aged 12 to 23 months was planned to be enrolled and randomized 1:1 (300 in the VARIVAX PE34 process vaccination group, 300 in the VARIVAX [2016 CP] vaccination group). The children should have been in good health based on medical history. Additionally, all subjects should not have clinical history for varicella, HZ, measles, mumps, and rubella-infections nor had a vaccination.

Treatments

Study Vaccinations

Vaccine	Dose/Potency	Dose Frequency	Route of Administration	Vaccination Regimen	Use
VARIVAX PE34 process (Group 1)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Investigational
VARIVAX (2016 CP) (Group 2)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Standard of care
M-M-R II (Groups 1 and 2)	0.5 mL after reconstitution	2 doses; 3 months between each dose	Subcutaneous injection	Visit 1 (Day 1) and Visit 3 (Week 13 [Days 91-105])	Standard of care

Study vaccinations were administered on the day of randomization or as close as possible to the date on which the participant was allocated/assigned.

Blood Sample Collection for Antibody Measurement

A 3-mL blood sample will be obtained from all subjects just before vaccination at Visit 1 (Day 1) and at Visit 2 (Day 43 [+14 days] Postvaccination 1). For all subjects at Visit 1 (Day 1), it is mandatory to collect a blood sample before a subject is randomized. Subjects must not be randomized into the trial if a blood sample cannot be obtained.

Outcomes/endpoints

Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated for between-group differences are described below.

Immunogenicity Endpoints

The primary endpoints for VZV immunogenicity will be the antibody response rates and GMTs after the first dose of VARIVAX in subjects who were initially seronegative to VZV at baseline.

The response rate and GMT endpoints and the criteria for baseline seronegativity are defined below:

- The response rate is the percentage of subjects with VZV antibody titer ≥5 gpELISA units/mL 6 weeks Postvaccination 1 among subjects who were seronegative to VZV (titer <1.25 gpELISA units/mL) at baseline.

- The postvaccination antibody GMTs 6 weeks Postvaccination 1.

In addition, the VZV seroconversion rate (defined as the proportion of subjects with baseline VZV titer <1.25 gpELISA units/mL and with postvaccination VZV titer ≥1.25 gpELISA units/mL) will be summarized after the first dose. For subjects who are initially seropositive (baseline VZV antibody titer ≥1.25 gpELISA units/mL), the geometric mean fold rise (GMFR) and the percentage of subjects achieving ≥4-fold rise in antibody titer from baseline will be summarized after the first dose.

Safety Endpoints

The key safety endpoints evaluated as Tier 1 events are as follows: the rate of elevated temperature from Days 1 to 42 after each vaccination; varicella-, zoster-, measles-, or rubella-like rashes or

mumps-like symptoms, and all injection-site rashes occurring within Days 1 to 42 after each vaccination, and all solicited injection-site reactions (redness, swelling, pain/tenderness) occurring within Days 1 to 5 after each vaccination.

Statistical Methods

The primary immunogenicity analyses were based on the Per-protocol population. A supportive summary and analysis for VZV immunogenicity was based on the Full Analysis Set.

For the primary hypothesis 1 based on antibody response rate, VARIVAX PE34 process was considered non-inferior to VARIVAX (2016 CP) if the lower bound of the 2-sided 95% CI for the difference in rates (Group 1 minus Group 2) excluded a decrease of 10 percentage points or more. For the primary hypothesis 2, based on GMT ratios, VARIVAX PE34 process was considered non-inferior to VARIVAX (2016 CP) if the lower bound of the 2-sided 95% CI of the GMT ratio (Group 1/Group 2) was >0.67. For the primary hypothesis 3, VARIVAX PE34 process was considered acceptable if the lower bound of the 2-sided 95% CI for the response rate was above 76.0%.

Results

Recruitment/ Number analysed

Across 35 study sites in the US, a total of 622 participants were screened and 600 were randomized to receive either VARIVAX PE34 process given concomitantly with M-M-R II (hereafter referred to as the PE34 group), or VARIVAX (2016 commercial product) given concomitantly with M-M-R II (hereafter referred to as the 2016 CP group) and [Table 1].

Almost all (599/600; 99.8%) randomized participants received at least 1 dose of study vaccine. One participant who was randomized to the PE34 group discontinued from the study prior to receiving the assigned vaccine and was not included in the immunogenicity or safety analyses. Overall, 9.8% of participants discontinued the study [Table 1]. The most common reasons for discontinuation from the study were lost to follow-up and withdrawal by parent/guardian or participant.

Of the participants who received at least 1 dose of study vaccine, the majority (558/599; 93.2%) completed the protocol-specified 2-dose vaccination regimen [Table 1]. The 3 most common reasons for discontinuation of study vaccination were withdrawal by parent/guardian, lost to follow-up, and other reasons. The number of participants who discontinued study vaccination or withdrew from the study was generally comparable for the 2 vaccination groups and [Table 1].

Table 1 Disposition of subjects

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
	n	(%)	n	(%)	n	(%)
Not Randomized					22	
Subjects in population	300		300		600	
Vaccinated at						
Vaccination 1	299	(99.7)	300	(100.0)	599	(99.8)
Vaccination 2	276	(92.0)	282	(94.0)	558	(93.0)
Status for Trial						
Completed	268	(89.3)	273	(91.0)	541	(90.2)
Discontinued	32	(10.7)	27	(9.0)	59	(9.8)
Lost To Follow-Up	15	(5.0)	16	(5.3)	31	(5.2)
Other	2	(0.7)	0	(0.0)	2	(0.3)
Physician Decision	1	(0.3)	0	(0.0)	1	(0.2)
Withdrawal By Parent/Guardian	12	(4.0)	11	(3.7)	23	(3.8)
Withdrawal By Subject	2	(0.7)	0	(0.0)	2	(0.3)
Status for Study Medication in Trial						
Started	299		300		599	
Completed	276	(92.3)	282	(94.0)	558	(93.2)
Discontinued	23	(7.7)	17	(5.7)	40	(6.7)
Adverse Event	1	(0.3)	0	(0.0)	1	(0.2)
Lost To Follow-Up	4	(1.3)	5	(1.7)	9	(1.5)
Other	6	(2.0)	3	(1.0)	9	(1.5)
Physician Decision	1	(0.3)	0	(0.0)	1	(0.2)
Withdrawal By Parent/Guardian	11	(3.7)	9	(3.0)	20	(3.3)
Status Not Recorded	0	(0.0)	1	(0.3)	1	(0.2)
Discontinued Between Visit 1 (Vaccination 1) and Visit 2						
Started	300		300		600	
Completed	290	(96.7)	289	(96.3)	579	(96.5)
Discontinued	9	(3.0)	11	(3.7)	20	(3.3)
Lost To Follow-Up	0	(0.0)	3	(1.0)	3	(0.5)
Physician Decision	1	(0.3)	0	(0.0)	1	(0.2)
Withdrawal By Parent/Guardian	8	(2.7)	8	(2.7)	16	(2.7)
Status Not Recorded	1	(0.3)	0	(0.0)	1	(0.2)
Discontinued Between Visit 2 and Visit 3 (Vaccination 2)						
Started	290		289		579	

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
	n	(%)	n	(%)	n	(%)
Discontinued Between Visit 2 and Visit 3 (Vaccination 2)						
Completed	282	(97.2)	285	(98.6)	567	(97.9)
Discontinued	7	(2.4)	4	(1.4)	11	(1.9)
Lost To Follow-Up	4	(1.4)	2	(0.7)	6	(1.0)
Withdrawal By Parent/Guardian	3	(1.0)	2	(0.7)	5	(0.9)
Status Not Recorded	1	(0.3)	0	(0.0)	1	(0.2)
Discontinued Between Visit 3 (Vaccination 2) and Visit 4						
Started	283		285		568	
Completed	274	(96.8)	282	(98.9)	556	(97.9)
Discontinued	9	(3.2)	3	(1.1)	12	(2.1)
Lost To Follow-Up	6	(2.1)	3	(1.1)	9	(1.6)
Other	2	(0.7)	0	(0.0)	2	(0.4)
Withdrawal By Subject	1	(0.4)	0	(0.0)	1	(0.2)
Discontinued Between Visit 4 and Last phone call						
Started	275		282		557	
Completed	268	(97.5)	273	(96.8)	541	(97.1)
Discontinued	7	(2.5)	9	(3.2)	16	(2.9)
Lost To Follow-Up	5	(1.8)	8	(2.8)	13	(2.3)
Withdrawal By Parent/Guardian	1	(0.4)	1	(0.4)	2	(0.4)
Withdrawal By Subject	1	(0.4)	0	(0.0)	1	(0.2)

CHMP comment
A dropout rate of around 10 % between enrolled and completed subjects is very common in paediatric vaccination trials. The dropout rate was comparable between both vaccination groups.

Baseline data

Baseline characteristics were comparable for the 2 vaccination groups [Table 2]. The median age of participants was 12.0 months and the majority of participants were white and of non-Hispanic or Latino ethnicity. Approximately equal proportions of participants were male and female.

Table 2 Subject Characteristics (All Randomized Subjects)

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	300		300		600	
Gender						
Male	147	(49.0)	173	(57.7)	320	(53.3)
Female	153	(51.0)	127	(42.3)	280	(46.7)
Age (Months)						
≤23 Months	300	(100.0)	300	(100.0)	600	(100.0)
Mean	13.0		13.2		13.1	
SD	1.4		1.7		1.6	
Median	12.0		12.0		12.0	
Range	12 to 19		12 to 23		12 to 23	
Race						
American Indian Or Alaska Native Asian Black Or African American Multi-Racial Native Hawaiian Or Other Pacific Islander White	PPD					
Ethnicity						
Hispanic Or Latino	46	(15.3)	60	(20.0)	106	(17.7)
Not Hispanic Or Latino	254	(84.7)	237	(79.0)	491	(81.8)
Not Reported	0	(0.0)	2	(0.7)	2	(0.3)
Unknown	0	(0.0)	1	(0.3)	1	(0.2)

Baseline Serostatus

The majority of participants in each vaccination group had an initial VZV antibody titer <1.25 gpELISA units/mL. The distribution of baseline serostatuses was comparable for the 2 vaccination groups [Table 3].

Table 3 Distribution of Baseline Serostatus for VZV (All Randomized Subjects)

	VARIVAX™ PE34 + M-M-R™ II (N=300)		VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		Total (N=600)	
	n	(%)	n	(%)	n	(%)
<1.25 gpELISA units/mL	264	(88.0)	258	(86.0)	522	(87.0)
≥1.25 gpELISA units/mL	35	(11.7)	42	(14.0)	77	(12.8)

N = Number of subjects randomized in the vaccination group.
n = Number of subjects in the indicated category.
Percentages were calculated based on n/N.
VZV = varicella-zoster virus.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

CHMP comment
The percentages of seropositive and seronegative subjects were equally distributed in both cohorts.

Medical History and Concurrent Illnesses

The 5 most frequently reported medical history conditions overall, by preferred term, included upper respiratory tract infection, gastroesophageal reflux disease, otitis media, otitis media acute, and diaper dermatitis. The incidence of reported conditions was generally comparable for the vaccination groups.

Concomitant Medications

Overall, 74.7% of participants received 1 or more concomitant medications from Day 1 to Day 42 Post-dose and 64.2% of participants received 1 or more concomitant medications from Day 1 to Day 42 Post-dose 2. The 3 most frequently reported concomitant medications prior to each dose, by medication class, included analgesics, anti-inflammatory and antirheumatic products, and antibacterials for systemic use. The incidence of reported concomitant medications was comparable for the 2 vaccination groups.

Concomitant Vaccinations

Overall, 7 (1.2%) participants received 1 or more concomitant vaccinations from Day 1 to Day 42 Postdose 1 [***Table 4***] and 7 (1.3%) participants received 1 or more concomitant vaccinations from Day 1 to Day 42 Postdose 2 [***Table 5***]. Concomitant vaccines reported included those that are recommended as routine paediatric vaccinations.

Table 4 Subjects With Specific Concomitant Vaccinations (Incidence > 0% in One or More Vaccination Groups) From Days 1 to 42 Post-dose 1 (All Randomized Subjects)

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	300		300		600	
With one or more concomitant vaccinations	0	(0.0)	7	(2.3)	7	(1.2)
With no concomitant vaccinations	300	(100.0)	293	(97.7)	593	(98.8)
antiinfectives for systemic use						
vaccines	**0**	**(0.0)**	**7**	**(2.3)**	**7**	**(1.2)**
Hib conj vaccine (unspecified carrier)	0	(0.0)	2	(0.7)	2	(0.3)
diphtheria toxoid (+) pertussis acellular vaccine (unspecified) (+) tetanus toxoid	0	(0.0)	2	(0.7)	2	(0.3)
hepatitis A virus vaccine (unspecified)	0	(0.0)	3	(1.0)	3	(0.5)
hepatitis B virus vaccine (unspecified)	0	(0.0)	1	(0.3)	1	(0.2)
influenza virus split virion 4v vaccine inactivated	0	(0.0)	1	(0.3)	1	(0.2)
influenza virus vaccine (unspecified)	0	(0.0)	2	(0.7)	2	(0.3)
pneumococcal 4 6B 9V 14 18C 19F 23F conj vaccine (CRM197)	0	(0.0)	1	(0.3)	1	(0.2)
pneumococcal vaccine (unspecified)	0	(0.0)	1	(0.3)	1	(0.2)
poliovirus vaccine inactivated (unspecified)	0	(0.0)	1	(0.3)	1	(0.2)

Every subject is counted a single time for each applicable specific concomitant vaccination. A subject with multiple concomitant vaccinations within a vaccination category is counted a single time for that category.

A vaccination class or specific vaccination appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Table 5 Subjects With Specific Concomitant Vaccinations (Incidence > 0% in One or More Vaccination Groups) From Days 1 to 42 Post-dose 2 (All Randomized Subjects)

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	276		282		558	
With one or more concomitant vaccinations	1	(0.4)	6	(2.1)	7	(1.3)
With no concomitant vaccinations	275	(99.6)	276	(97.9)	551	(98.7)
antiinfectives for systemic use						
vaccines	**1**	**(0.4)**	**6**	**(2.1)**	**7**	**(1.3)**
Hib conj vaccine (unspecified carrier)	1	(0.4)	1	(0.4)	2	(0.4)
diphtheria toxoid (+) pertussis acellular vaccine (unspecified) (+) tetanus toxoid	1	(0.4)	3	(1.1)	4	(0.7)
hepatitis A virus vaccine (unspecified)	0	(0.0)	3	(1.1)	3	(0.5)
influenza virus vaccine (unspecified)	1	(0.4)	1	(0.4)	2	(0.4)
pneumococcal 4 6B 9V 14 18C 19F 23F conj vaccine (CRM197)	1	(0.4)	0	(0.0)	1	(0.2)
pneumococcal conj vaccine (unspecified)	0	(0.0)	1	(0.4)	1	(0.2)

Every subject is counted a single time for each applicable specific concomitant vaccination. A subject with multiple concomitant vaccinations within a vaccination category is counted a single time for that category.

A vaccination class or specific vaccination appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

CHMP comment

At first vaccination only subjects were concomitantly vaccinated in the VARIVAX(2016 CP)+MMRII-group and none in the VARIVAX PE34+ MMRII-group. After second vaccination only 1 subject was concomitantly vaccinated in the VARIVAX PE34+MMRII-group versus 6 subjects in the VARIVAX(2016 CP)+ MMRII-group. The ratio between both groups was quite unbalanced with 2.3 % or 2.1% and none or 0.4 % in the other group.

Key Features of the Participant Population

A total of 600 participants were randomized in the study (300 to the PE34 group and 300 to the 2016 CP group. All but 1 (599/600; 99.8%) randomized participants received at least 1 dose of study vaccine and were included in the ASaT population for the safety analyses and most (90.2%) completed the study. The majority of participants in the ASaT population (558/599; 93.2%) completed the protocol-specified 2-dose vaccination regimen. The number of participants who discontinued study vaccination or discontinued from the study was generally comparable for the 2 vaccination groups.

A total of 484/600 (80.7%) participants contributed to the primary immunogenicity analyses (PP population). The distribution of participants excluded from the PP population was comparable for the 2 vaccination groups.

Supportive immunogenicity analyses were conducted using the FAS population, which consisted of all randomized participants with a valid serology measurement, regardless of protocol deviations.

Safety analyses were based on the ASaT population. Baseline characteristics were comparable for the 2 vaccination groups [Table 2]. Participants had a median age of 12.0 months (Age range: 12 to 23 months) at the time of randomization, with approximately equal proportions of male and female participants. The majority of participants were White and of non-Hispanic or Latino ethnicity.

Efficacy results

Immunogenicity Results for the V210-A03 Study

Primary Efficacy Endpoints

The study met the criteria for the 3 hypotheses supporting the primary objectives, as follows.

Non-inferiority of Immune Response Based on VZV Antibody Response Rate at 6 weeks Post-dose 1

Non-inferiority of PE34 compared to 2016 CP was demonstrated based on the VZV antibody response rate at 6 weeks Postdose 1 in the PP population, as the lower bound of the 2-sided 95% CI for the treatment difference in response rate (PE34 group – 2016 CP group) excluded a decrease of 10 percentage points or more [Table 6]. The prespecified success criterion for this hypothesis was met (p<0.001). The analysis for the FAS showed comparable results.

Table 6 Statistical Analysis (Non-inferiority) of Antibody Response Rates to VZV at 6 Weeks Post-dose 1 (Per-Protocol Population)

		VARIVAX™ PE34 + M-M-R™ II (N=299)		VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		Risk Difference vs VARIVAX™ (2016 CP) + M-M-R™ II (95% Confidence Interval)†	Non-inferiority Conclusion†
Antibody	Parameter	n	Observed Response	n	Observed Response		
VZV	Percent Subjects ≥ 5gpELISA units/mL	245	98.4% (241/245)	239	98.3% (235/239)	0.0% (-2.7%, 2.8%)	Non-inferior (p<0.001)

† The 2-sided 95% CI is calculated using the Miettinen and Nurminen unconditional asymptotic method. The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the risk difference excluding a decrease of 10.0 percentage points or more, which corresponds to a one-sided p-value < 0.025.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seronegative antibody titer (< 1.25 gpELISA units/mL) at baseline and postvaccination serology contributing to the per-protocol analysis.
VZV = varicella-zoster virus.
CI = Confidence interval.
CP = Commercial product.
PE = Passage extension.

Non-inferiority of Immune Response Based on VZV Antibody GMTs at 6 weeks Post-dose 1

Non-inferiority of PE34 compared to 2016 CP was demonstrated based on the VZV antibody GMTs at 6 weeks Post-dose 1 in the PP population as the lower bound of the 2-sided 95% CI for the GMT ratio (PE34 group/2016 CP group) was greater than 0.67 [Table 7]. The prespecified success criterion for this hypothesis was met (p<0.001). The analysis for the FAS showed comparable results.

Table 7 Statistical Analysis (Non-inferiority) of VZV Antibody GMT at 6 Weeks Post-dose 1 (Per-Protocol Population)

		VARIVAX™ PE34 + M-M-R™ II (N=299)		VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		Observed GMT Ratio vs VARIVAX™ (2016 CP) + M-M-R™ II†	Non-inferiority†
Antibody	Parameter	n	Observed GMT	n	Observed GMT	(95% Confidence Interval)	Conclusion
VZV	GMT	245	18.5	239	19.0	1.0 (0.9, 1.1)	Non-inferior (p<0.001)

† The 2-sided 95% CI is based on the natural log-transformed titers and the t-distribution. The conclusion of non-inferiority (similarity) is based on the lower bound of the 2-sided 95% CI for the GMT ratio being > 0.67, which corresponds to a one-sided p-value < 0.025.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seronegative antibody titer (<1.25gpELISA units/mL) at baseline and postvaccination serology contributing to the per-protocol analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
VZV = varicella-zoster virus.
CI = Confidence interval.
GMT = Geometric mean titer.
CP = Commercial product.
PE = Passage extension.

Acceptability of Immune Response Based on VZV Antibody Response Rate at 6 weeks Postdose 1

VARIVAX PE34 induced an acceptable VZV antibody response at 6 weeks Post-dose 1 in the PP population as the lower bound of the one-sided 95% CIs of response rates was greater than 76% [Table 8]. The prespecified success criterion for this hypothesis was met (p<0.001). The prespecified success criterion for this hypothesis was met. The analysis for the FAS showed comparable results.

Table 8 Statistical Analysis (Acceptability) of Antibody Response Rates to VZV at 6 Weeks Post-dose 1 in VARIVAX PE34 + M-M-R II Group (Per-Protocol Population)

Antibody	Parameter	VARIVAX™ PE34 + M-M-R™ II (N=299)			Acceptability† Conclusion
		n	Observed Response	95% Confidence Interval†	
VZV	Percent Subjects ≥5 gpELISA units/mL	245	98.4% (241/245)	(95.9%,99.6%)	Acceptable (p<0.001)

† The 1-sample, 2-sided 95% CI for the response rate is computed using the exact CI method for a single binomial proportion. The conclusion of acceptability is based on the lower bound of the 95% CI being >76%, which corresponds to a one-sided p-value < 0.025.

N = Number of subjects vaccinated in the vaccination group at Dose 1.

n = Number of subjects with seronegative antibody titer (<1.25gpELISA units/mL) at baseline and postvaccination serology contributing to the per-protocol analysis.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

VZV = varicella-zoster virus.

CI = Confidence interval.

PE = Passage extension.

Secondary Immunogenicity Endpoints

Postdose 1 Antibody Response to VZV

The proportion of participants with VZV antibody titers ≥5 gpELISA units/mL at 6 weeks Post-dose 1 in the PP population was comparable for the 2 vaccination groups [Table 9].

Table 9 Summary of Antibody Responses to VZV at 6 Weeks Post-dose 1 (Per-Protocol Population)

		VARIVAX™ PE34 + M-M-R™ II (N=299)			VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		
Antibody	Parameter	n	Observed Response	95% Confidence Interval	n	Observed Response	95% Confidence Interval
VZV	Percent subjects ≥ 1.25gpELISA units/mL[†]	245	100.0% (245/245)	(98.5%, 100.0%)	239	100.0% (239/239)	(98.5%, 100.0%)
	Percent subjects ≥ 5gpELISA units/mL[†]	245	98.4% (241/245)	(95.9%, 99.6%)	239	98.3% (235/239)	(95.8%, 99.5%)
	GMT [‡]	245	18.5	(17.1, 20.1)	239	19.0	(17.6, 20.5)

[†] Confidence interval computed using the exact CI method for a single binomial proportion.
[‡] Confidence interval based on the natural log-transformed titers and the t-distribution.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seronegative antibody titer (<1.25gpELISA units/mL) at baseline and postvaccination serology contributing to per-protocol analysis.
VZV = varicella-zoster virus.
GMT = Geometric mean titer.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CP = Commercial product.
PE = Passage extension.

The postvaccination antibody GMTs for VZV at 6 weeks Post-dose 1 in the PP population were also comparable. The VZV seroconversion rate (defined as the proportion of participants with baseline VZV antibody titer <1.25 gpELISA units/mL and with postvaccination VZV antibody titer ≥1.25 gpELISA units/mL) at 6 weeks Post-dose 1 in the PP population was 100% for both vaccination groups. The analysis for the FAS showed comparable results [Table 10].

Table 10 Summary of Antibody Responses to VZV at 6 Weeks Postdose 1 (Full Analysis Set)

		VARIVAX™ PE34 + M-M-R™ II (N=299)			VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		
Antibody	Parameter	n	Observed Response	95% Confidence Interval	n	Observed Response	95% Confidence Interval
VZV	Percent subjects ≥ 1.25gpELISA units/mL[†]	251	100.0% (251/251)	(98.5%, 100.0%)	241	100.0% (241/241)	(98.5%, 100.0%)
	Percent subjects ≥ 5gpELISA units/mL[†]	251	98.4% (247/251)	(96.0%, 99.6%)	241	98.3% (237/241)	(95.8%, 99.5%)
	GMT [‡]	251	18.7	(17.3, 20.2)	241	19.0	(17.6, 20.5)

[†] Confidence interval computed using the exact CI method for a single binomial proportion.
[‡] Confidence interval based on the natural log-transformed titers and the t-distribution.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seronegative antibody titer (<1.25gpELISA units/mL) at baseline and postvaccination serology contributing to full analysis set.
VZV = varicella-zoster virus.
GMT = Geometric mean titer.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CP = Commercial product.
PE = Passage extension.

The overall pattern of the responses seen in the PP population analysis was comparable in the analyses conducted by gender and race with no notable differences between vaccination groups [Table 11].

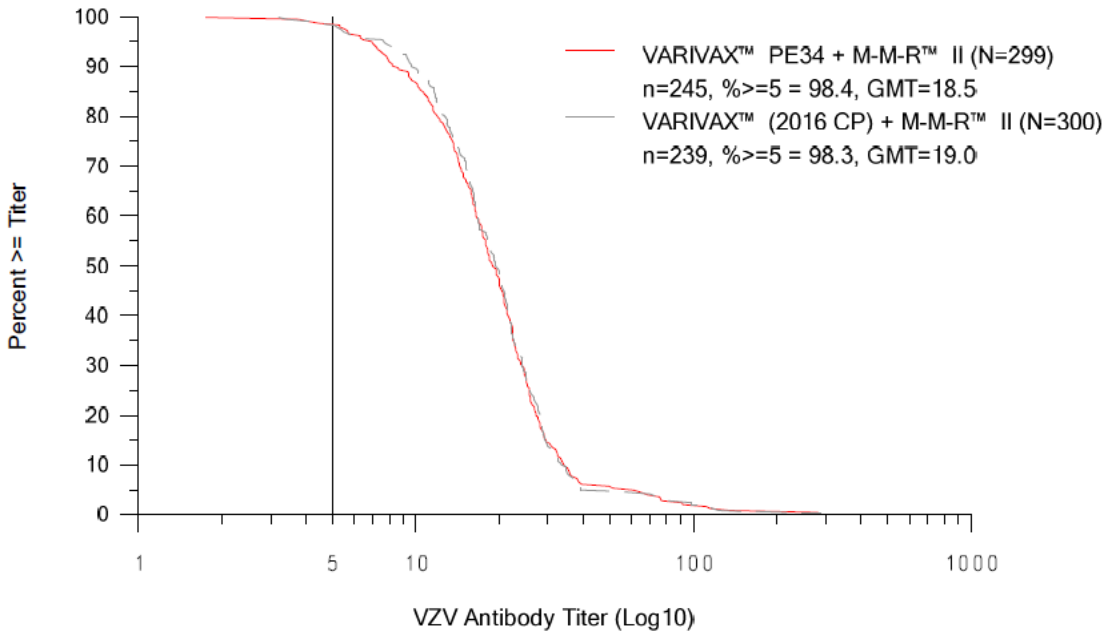
Table 11 Summary of Antibody Responses to VZV at 6 Weeks Post-dose 1 by Gender(Per-Protocol Population)

		VARIVAX™ PE34 + M-M-R™ II (N=299)		VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		Risk Difference vs VARIVAX™ (2016 CP) + M-M-R™ II (95% Confidence Interval)[†]
Gender	Parameter	n	Observed Response	n	Observed Response	
Male	Percent ≥ 1.25gpELISA units/mL[†]	120	100.0% (120/120)	131	100.0% (131/131)	0.0 (-3.1, 2.9)
	Percent ≥ 5gpELISA units/mL[†]	120	99.2% (119/120)	131	98.5% (129/131)	0.7 (-3.2, 4.7)
	GMT [‡]	120	18.0	131	19.1	0.9 (0.8, 1.1)
Female	Percent ≥ 1.25gpELISA units/mL[†]	125	100.0% (125/125)	108	100.0% (108/108)	0.0 (-3.0, 3.4)
	Percent ≥ 5gpELISA units/mL[†]	125	97.6% (122/125)	108	98.1% (106/108)	-0.5 (-5.2, 4.4)
	GMT [‡]	125	19.1	108	18.9	1.0 (0.9, 1.2)

[†]Confidence interval computed using the Miettinen and Nurminen unconditional asymptotic method.
[‡]Confidence interval based on the natural log-transformed titers and the t-distribution.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seronegative antibody titer (<1.25gpELISA units/mL) at baseline and postvaccination serology contributing to the per-protocol analysis.
VZV = varicella-zoster virus.
GMT = Geometric mean titer.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CP = Commercial product.
PE = Passage extension.

Graphical display of the reverse cumulative distribution function of Post-dose 1 VZV antibody titers in the PP population indicates that the immune responses to VZV vaccine were comparable for the 2 vaccination groups [Figure 1].

Figure 1 Reverse Cumulative Distribution Function of Post-dose 1 VZV Antibody Titers (Per-Protocol Population)



Immunogenicity in Participants Initially Seropositive Who Satisfy All Other Requirements for Inclusion in the PP Population – Post-dose 1

Within the PP population, a total of 71 participants were identified as seropositive at baseline (VZV antibody ≥1.25gpELISA units/mL); a summary of immunogenicity for these participants can be found in [Table 12]. For participants who were initially seropositive to VZV, there were no notable differences between the 2 vaccination groups in the antibody response rates (proportion of participants ≥5 gpELISA units/mL), GMTs, GMFR, or proportion of participants with ≥4-fold rise at 6 weeks Post-dose 1 compared to baseline.

Table 12 Summary of Immunogenicity to VZV in Subjects Initially Seropositive to VZV Antibody at 6 Weeks Post-dose 1 (Per-Protocol Population)

			VARIVAX™ PE34 + M-M-R™ II (N=299)			VARIVAX™ (2016 CP) + M-M-R™ II (N=300)		
Antibody	Time Point	Parameter	n	Observed Response	95% Confidence Interval	n	Observed Response	95% Confidence Interval
VZV	Baseline	GMT	31	2.5	(1.9, 3.3)	40	1.8	(1.6, 2.1)
	Postdose 1	Percent subjects ≥ 5gpELISA units/mL	31	100.0% (31/31)	(88.8%, 100.0%)	40	97.5% (39/40)	(86.8%, 99.9%)
		GMT	31	16.5	(12.3, 22.1)	40	13.2	(11.4, 15.2)
		GMFR	31	6.5	(5.0, 8.5)	40	7.2	(5.9, 8.9)
		Percent ≥4-fold rise[†]	31	80.6% (25/31)	(62.5%, 92.5%)	40	82.5% (33/40)	(67.2%, 92.7%)

[†] Fold rise is measured from pre-vaccination (Baseline).
Confidence interval is calculated if there are at least 5 subjects who are seropositive.
N = Number of subjects vaccinated in the vaccination group at Dose 1.
n = Number of subjects with seropositive antibody titer (≥1.25gpELISA units/mL) at baseline and postvaccination serology contributing to the per-protocol analysis.
VZV = varicella-zoster virus.
GMT = Geometric mean titer.
GMFR = Geometric mean fold rise.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
CP = Commercial product.
PE = Passage extension.

The analysis for the FAS showed comparable results.

Safety results

All but 1 (599/600; 99.8%) randomized participants received at least 1 dose of study vaccine (Vaccination 1), and the majority (558/599, 93.2%) completed the protocol-specified 2-dose vaccination regimen (Vaccination 1 and Vaccination 2).

Summary of Adverse Events

The majority of participants experienced at least 1 AE from Days 1 to 42 Postdose 1 or Postdose 2 [Table 13]. The overall proportions of participants who reported AEs Postdose 1 and Postdose 2 were comparable for the 2 vaccination groups. The incidence of injection-site and systemic AEs, as well as fever and vaccine-specific rashes and mumps-like symptoms, was comparable between the vaccination groups. Fewer than 45% of participants in each vaccination group experienced injection-site AEs from Days 1 to 42 Postdose 1 or Postdose 2, whereas the majority (approximately 85%) in each vaccination group experienced systemic AEs [Table 13]. No participants discontinued vaccine due to an AE during Days 1 to 42 Postdose 1 or Postdose 2.

Few participants experienced SAEs during the study, either during the safety follow-up period (4 participants in the PE34 group and 1 participant in the 2016 CP group from Day 1 to Day 42 Postdose 1 or Postdose 2) [Table 13] or through the safety follow-up and extended safety periods (6 participants in each vaccination group from Day 1 to Day 180 Postdose 2). No SAEs were considered to be vaccine-related (to VARIVAX or M-M-R II) and no participants discontinued study vaccine or discontinued from the study due to an SAE. No participants died during the study.

The safety profile was comparable for VARIVAX and M-M-R II, with regard to incidence of injection-site AEs and SAEs, and no differences were observed in any other safety parameters. No changes to the current safety profile of concomitant administration of VARIVAX and M-M-R II are indicated.

Table 13 Analysis of Adverse Event Summary Days 1 to 42 Postdose 1 or Postdose 2 (All Subjects as Treated Population)

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population with follow-up	299		300		
with one or more adverse events	269	(90.0)	265	(88.3)	1.6 (-3.4, 6.7)
injection-site	132	(44.1)	129	(43.0)	1.1 (-6.8, 9.1)
non-injection-site	256	(85.6)	254	(84.7)	1.0 (-4.8, 6.7)
with no adverse event	30	(10.0)	35	(11.7)	-1.6 (-6.7, 3.4)
with vaccine-related[‡] adverse events	168	(56.2)	163	(54.3)	1.9 (-6.1, 9.8)
injection-site	132	(44.1)	129	(43.0)	1.1 (-6.8, 9.1)
non-injection-site	87	(29.1)	83	(27.7)	1.4 (-5.8, 8.7)
with non-serious adverse events	269	(90.0)	265	(88.3)	1.6 (-3.4, 6.7)
with serious adverse events	4	(1.3)	1	(0.3)	1.0 (-0.7, 3.1)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
who died	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
who died due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0.0 (-1.3, 1.3)

[†] Based on Miettinen & Nurminen method.

[‡] Determined by the investigator to be related to the vaccine.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

CHMP comment
The frequencies of reported AEs were comparable in both groups. Only SAEs were reported in a higher frequency in the VARIVAX PE34-group with 4 subjects versus 1 subject in the VARIVAX (2016 CP)-group. All reported SAEs were not considered to be vaccine related.

Common adverse events

Injection-site Adverse Events
All injection-site AEs were considered related to the vaccination, either VARIVAX and/or M-M-R II.

The incidence of injection-site AEs reported from Days 1 to 42 after each dose was comparable between the 2 vaccination groups for both VARIVAX and M-M-R II [Table 14, Table 15, Table 16, and Table 17].
The 3 most frequently reported injection-site AEs from Days 1 to 42 after each dose were injection-site erythema (redness), injection-site pain (pain/tenderness/soreness), and injection-site swelling in both vaccination groups for both VARIVAX and M-M-R II.
Injection-site AEs related to VARIVAX were reported by 31.1% of participants in the PE34 group and 29.7% of participants in the 2016 CP group from Days 1 to 42 Postdose 1 [Table 14] and by 25.7% of participants in the PE34 group and 25.5% of participants in the 2016 CP group from Day 1 to Day 42 Postdose 2 [Table 15].

Table 14 Analysis of Subjects With Injection Site Adverse Events (Incidence ⩾ 4 Subjects in One or More Vaccination Groups) Days 1 to 42 Post-dose 1 VARIVAX

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	299		300		
with one or more injection site adverse events	93	(31.1)	89	(29.7)	1.4 (-5.9, 8.8)
Injection site bruising	4	(1.3)	5	(1.7)	-0.3 (-2.7, 1.9)
Injection site erythema	44	(14.7)	42	(14.0)	0.7 (-5.0, 6.4)
Injection site induration	6	(2.0)	3	(1.0)	1.0 (-1.1, 3.4)
Injection site mass	9	(3.0)	3	(1.0)	2.0 (-0.3, 4.7)
Injection site pain	41	(13.7)	38	(12.7)	1.0 (-4.4, 6.5)
Injection site rash	7	(2.3)	11	(3.7)	-1.3 (-4.4, 1.5)
Injection site swelling	17	(5.7)	17	(5.7)	0.0 (-3.8, 3.9)

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Table 15 Analysis of Subjects With Injection Site Adverse Events (Incidence ⩾ 4 Subjects in One or More Vaccination Groups) Days 1 to 42 Post-dose 2 VARIVAX

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	276		282		
with one or more injection site adverse events	71	(25.7)	72	(25.5)	0.2 (-7.1, 7.5)
with no injection site adverse events	205	(74.3)	210	(74.5)	-0.2 (-7.5, 7.1)
Injection site erythema	54	(19.6)	56	(19.9)	-0.3 (-6.9, 6.4)
Injection site pain	25	(9.1)	29	(10.3)	-1.2 (-6.2, 3.8)
Injection site swelling	28	(10.1)	23	(8.2)	2.0 (-2.9, 6.9)

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Injection-site AEs related to M-M-R II were reported by 22.7% of participants in the PE34 group and 20.7% of participants in the 2016 CP group from Day 1 to Day 42 Postdose 1 [Table 16] and by 18.1% of participants in both vaccination groups Postdose 2 [Table 17].

Table 16 Analysis of Subjects With Injection Site Adverse Events (Incidence ⩾ 4 Subjects in One or More Vaccination Groups) Days 1 to 42 Post-dose 1 M-M-R II

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	299		300		
with one or more injection site adverse events	68	(22.7)	62	(20.7)	2.1 (-4.5, 8.7)
Injection site bruising	5	(1.7)	8	(2.7)	-1.0 (-3.7, 1.5)
Injection site erythema	26	(8.7)	26	(8.7)	0.0 (-4.6, 4.7)
Injection site pain	36	(12.0)	34	(11.3)	0.7 (-4.5, 5.9)
Injection site swelling	10	(3.3)	15	(5.0)	-1.7 (-5.1, 1.7)

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Table 17 Analysis of Subjects With Injection Site Adverse Events (Incidence ⩾ 4 Subjects in One or More Vaccination Groups) Days 1 to 42 Post-dose 2 M-M-R II

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	276		282		
with one or more injection site adverse events	50	(18.1)	51	(18.1)	0.0 (-6.4, 6.5)
Injection site bruising	4	(1.4)	4	(1.4)	0.0 (-2.3, 2.4)
Injection site erythema	29	(10.5)	30	(10.6)	-0.1 (-5.3, 5.1)
Injection site pain	24	(8.7)	24	(8.5)	0.2 (-4.6, 5.0)
Injection site swelling	9	(3.3)	9	(3.2)	0.1 (-3.1, 3.3)

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Solicited Injection-site Adverse Events (Days 1 to 5 Postdose 1 and Postdose 2)

The incidence of solicited injection-site AEs (erythema, swelling, pain) reported from Days 1 to 5 Postdose 1 and Postdose 2 was comparable between the 2 vaccination groups for both VARIVAX and M-M-R II [Table 18, Table 19,
Table 20, and Table 21]. In both vaccination groups, there was a higher incidence of injection-site erythema and injection-site swelling (for VARIVAX) and of injection-site erythema (for M-M-R II) Postdose 2 [Table 19,Table 21] compared to Postdose 1 [Table 18,
Table 20], but a lower incidence of injection-site pain Postdose 2 [Table 19, Table 21] compared to Postdose 1 [Table 18,
Table 20] for both VARIVAX and M-M-R II.

Table 18 Analysis of Subjects With VRC-Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 1 VARIVAX

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II	
	n	(%)	n	(%)	Estimate (95% CI)†	p-value†
Subjects in population with follow-up	299		300			
with one or more VRC-Solicited injection site adverse events	66	(22.1)	63	(21.0)	1.1 (-5.5, 7.7)	0.749
with no VRC-Solicited injection site adverse events	233	(77.9)	237	(79.0)	-1.1 (-7.7, 5.5)	0.749
Injection site erythema	29	(9.7)	32	(10.7)	-1.0 (-5.9, 4.0)	0.696
Injection site pain	40	(13.4)	38	(12.7)	0.7 (-4.7, 6.2)	0.796
Injection site swelling	9	(3.0)	17	(5.7)	-2.7 (-6.2, 0.7)	0.111

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
VRC = Vaccine report card.

Table 19 Analysis of Subjects With VRC-Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 2 VARIVAX

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II	
	n	(%)	n	(%)	Estimate (95% CI)†	p-value†
Subjects in population with follow-up	276		282			
with one or more VRC-Solicited injection site adverse events	70	(25.4)	71	(25.2)	0.2 (-7.0, 7.4)	0.960
with no VRC-Solicited injection site adverse events	206	(74.6)	211	(74.8)	-0.2 (-7.4, 7.0)	0.960
Injection site erythema	54	(19.6)	56	(19.9)	-0.3 (-6.9, 6.4)	0.931
Injection site pain	24	(8.7)	29	(10.3)	-1.6 (-6.6, 3.4)	0.523
Injection site swelling	28	(10.1)	23	(8.2)	2.0 (-2.9, 6.9)	0.415

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
VRC = Vaccine report card.

Table 20 Analysis of Subjects With VRC-Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 1 M-M-R II

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II	
	n	(%)	n	(%)	Estimate (95% CI)†	p-value†
Subjects in population with follow-up	299		300			
with one or more VRC-Solicited injection site adverse events	58	(19.4)	55	(18.3)	1.1 (-5.2, 7.4)	0.739
with no VRC-Solicited injection site adverse events	241	(80.6)	245	(81.7)	-1.1 (-7.4, 5.2)	0.739
Injection site erythema	23	(7.7)	25	(8.3)	-0.6 (-5.1, 3.8)	0.773
Injection site pain	36	(12.0)	34	(11.3)	0.7 (-4.5, 5.9)	0.788
Injection site swelling	10	(3.3)	15	(5.0)	-1.7 (-5.1, 1.7)	0.311

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
VRC = Vaccine report card.

Table 21 Analysis of Subjects With VRC-Solicited Injection Site Adverse Events (Incidence > 0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 2 M-M-R II

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II	
	n	(%)	n	(%)	Estimate (95% CI)†	p-value†
Subjects in population with follow-up	276		282			
with one or more VRC-Solicited injection site adverse events	48	(17.4)	48	(17.0)	0.4 (-5.9, 6.7)	0.908
with no VRC-Solicited injection site adverse events	228	(82.6)	234	(83.0)	-0.4 (-6.7, 5.9)	0.908
Injection site erythema	29	(10.5)	30	(10.6)	-0.1 (-5.3, 5.1)	0.960
Injection site pain	23	(8.3)	24	(8.5)	-0.2 (-4.9, 4.6)	0.940
Injection site swelling	9	(3.3)	9	(3.2)	0.1 (-3.1, 3.3)	0.963

† Based on Miettinen & Nurminen method.
Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
VRC = Vaccine report card.

By Intensity

All injection-site AEs reported from Days 1 to 5 Postdose 1 and Postdose 2 in both vaccination groups were mild to moderate in intensity for VARIVAX [Table 22, Table 23] and all but one (1 severe AE of injection-site pain Postdose 1 was reported in the PE34 group) were mild to moderate in intensity in both vaccination groups for M-M-R II [Table 24,Table 25].

Table 22 Subjects With Injection Site Adverse Events by Maximum Intensity (Incidence >0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 1 VARIVAX

	Intensity Grading	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
		n	(%)	n	(%)	n	(%)
Subjects in population with follow-up		299		300		599	
All Injection Site AEs	Total	47	(15.7)	40	(13.3)	87	(14.5)
	Mild	41	(13.7)	36	(12.0)	77	(12.9)
	Moderate	6	(2.0)	4	(1.3)	10	(1.7)
Injection site bruising	Total	4	(1.3)	3	(1.0)	7	(1.2)
	Mild	4	(1.3)	3	(1.0)	7	(1.2)
Injection site induration	Total	4	(1.3)	0	(0.0)	4	(0.7)
	Mild	4	(1.3)	0	(0.0)	4	(0.7)
Injection site pain	Total	40	(13.4)	38	(12.7)	78	(13.0)
	Mild	34	(11.4)	34	(11.3)	68	(11.4)
	Moderate	6	(2.0)	4	(1.3)	10	(1.7)
Injection site rash	Total	1	(0.3)	0	(0.0)	1	(0.2)
	Mild	1	(0.3)	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable specific injection site adverse event, and is classified according to the highest non-missing intensity grading.

A specific injection site adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Injection Site Swelling and Injection Site Erythema occurring from Day 1 to Day 5 postvaccination are not included in this report

Table 23 Subjects With Injection Site Adverse Events by Maximum Intensity (Incidence >0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 2 VARIVAX

	Intensity Grading	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
		n	(%)	n	(%)	n	(%)
Subjects in population with follow-up		276		282		558	
All Injection Site AEs	Total	28	(10.1)	33	(11.7)	61	(10.9)
	Mild	20	(7.2)	31	(11.0)	51	(9.1)
	Moderate	6	(2.2)	2	(0.7)	8	(1.4)
	Unknown	2	(0.7)	0	(0.0)	2	(0.4)
Injection site bruising	Total	1	(0.4)	2	(0.7)	3	(0.5)
	Mild	1	(0.4)	2	(0.7)	3	(0.5)
Injection site induration	Total	0	(0.0)	1	(0.4)	1	(0.2)
	Mild	0	(0.0)	1	(0.4)	1	(0.2)
Injection site mass	Total	2	(0.7)	1	(0.4)	3	(0.5)
	Mild	0	(0.0)	1	(0.4)	1	(0.2)
	Unknown	2	(0.7)	0	(0.0)	2	(0.4)
Injection site pain	Total	24	(8.7)	29	(10.3)	53	(9.5)
	Mild	18	(6.5)	27	(9.6)	45	(8.1)
	Moderate	6	(2.2)	2	(0.7)	8	(1.4)
Injection site pruritus	Total	1	(0.4)	0	(0.0)	1	(0.2)
	Mild	1	(0.4)	0	(0.0)	1	(0.2)
Injection site rash	Total	0	(0.0)	1	(0.4)	1	(0.2)
Injection site rash	Total	0	(0.0)	1	(0.4)	1	(0.2)
	Mild	0	(0.0)	1	(0.4)	1	(0.2)

Every subject is counted a single time for each applicable specific injection site adverse event, and is classified according to the highest non-missing intensity grading.

A specific injection site adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Injection Site Swelling and Injection Site Erythema occurring from Day 1 to Day 5 postvaccination are not included in this report

Table 24 Subjects With Injection Site Adverse Events by Maximum Intensity (Incidence >0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 1 M-M-R II

	Intensity Grading	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
		n	(%)	n	(%)	n	(%)
Subjects in population with follow-up		299		300		599	
All Injection Site AEs	Total	41	(13.7)	40	(13.3)	81	(13.5)
	Mild	34	(11.4)	36	(12.0)	70	(11.7)
	Moderate	6	(2.0)	3	(1.0)	9	(1.5)
	Severe	1	(0.3)	0	(0.0)	1	(0.2)
	Unknown	0	(0.0)	1	(0.3)	1	(0.2)
Injection site bruising	Total	4	(1.3)	8	(2.7)	12	(2.0)
	Mild	4	(1.3)	7	(2.3)	11	(1.8)
	Unknown	0	(0.0)	1	(0.3)	1	(0.2)
Injection site induration	Total	2	(0.7)	1	(0.3)	3	(0.5)
	Mild	2	(0.7)	1	(0.3)	3	(0.5)
Injection site pain	Total	36	(12.0)	34	(11.3)	70	(11.7)
	Mild	30	(10.0)	31	(10.3)	61	(10.2)
	Moderate	5	(1.7)	3	(1.0)	8	(1.3)
	Severe	1	(0.3)	0	(0.0)	1	(0.2)
Injection site rash	Total	1	(0.3)	0	(0.0)	1	(0.2)
	Moderate	1	(0.3)	0	(0.0)	1	(0.2)

Every subject is counted a single time for each applicable specific injection site adverse event, and is classified according to the highest non-missing intensity grading.

A specific injection site adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Injection Site Swelling and Injection Site Erythema occurring from Day 1 to Day 5 postvaccination are not included in this report

Table 25 Subjects With Injection Site Adverse Events by Maximum Intensity (Incidence >0% in One or More Vaccination Groups) Days 1 to 5 Post-dose 2 M-M-R II

	Intensity Grading	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Total	
		n	(%)	n	(%)	n	(%)
Subjects in population with follow-up		276		282		558	
All Injection Site AEs	Total	26	(9.4)	29	(10.3)	55	(9.9)
	Mild	22	(8.0)	26	(9.2)	48	(8.6)
	Moderate	4	(1.4)	2	(0.7)	6	(1.1)
	Unknown	0	(0.0)	1	(0.4)	1	(0.2)
Injection site bruising	Total	4	(1.4)	4	(1.4)	8	(1.4)
	Mild	4	(1.4)	3	(1.1)	7	(1.3)
	Unknown	0	(0.0)	1	(0.4)	1	(0.2)
Injection site mass	Total	0	(0.0)	1	(0.4)	1	(0.2)
	Mild	0	(0.0)	1	(0.4)	1	(0.2)
Injection site pain	Total	23	(8.3)	24	(8.5)	47	(8.4)
	Mild	19	(6.9)	22	(7.8)	41	(7.3)
	Moderate	4	(1.4)	2	(0.7)	6	(1.1)
Injection site rash	Total	0	(0.0)	1	(0.4)	1	(0.2)
	Mild	0	(0.0)	1	(0.4)	1	(0.2)

Every subject is counted a single time for each applicable specific injection site adverse event, and is classified according to the highest non-missing intensity grading.

A specific injection site adverse event appears on this report only if its incidence in one or more of the columns is greater than or equal to the percent incidence specified in the report title, after rounding.

Injection Site Swelling and Injection Site Erythema occurring from Day 1 to Day 5 postvaccination are not included in this report

CHMP comment

The intensity of injection site reactions was comparable in both vaccination groups for VARIVAX as well as the concomitantly administered M-M-RVAXPRO. The reported intensities were mostly assessed as mild and rare as moderate intensity. Only one subject reported severe injection site reaction after administration of M-M-RVAXPRO.

Injection-Site Adverse Events by Size

In both vaccination groups, most of the AEs of injection-site erythema and injection-site swelling reported from Day 1 to Day 5 after each dose of VARIVAX were 0 to ⩽1 inches in size. While there was a slightly higher frequency of erythema and swelling Postdose 2 compared to Postdose 1, there was no notable change in severity as assessed by size.

In both vaccination groups, most of the AEs of injection-site erythema and swelling reported from Day 1 to Day 5 Postdose 1 and Postdose 2 following vaccination with M-M-R II, were 0 to ⩽1 inches in size.

Systemic Adverse Events by Intensity

The incidence of systemic AEs reported from Days 1 to 42 Postdose 1 and Postdose 2 was generally comparable between the vaccination groups after each dose. Systemic AEs were reported for the majority of participants Postdose 1 and Postdose 2 in both vaccination groups, with a generally lower incidence Postdose 2 compared with Postdose 1.

Postdose 1, the most frequently reported (⩾10% in any vaccination group) systemic AEs were pyrexia, irritability, cough, rhinorrhea, otitis media, upper respiratory tract infection, diarrhea, teething, and nasopharyngitis.
Postdose 2, the most frequently reported (⩾10% in any vaccination group) systemic AEs were pyrexia and rhinorrhea.

The majority of systemic AEs in both vaccination groups were reported as mild to moderate in intensity from Day 1 to Day 42 Postdose 1 and Postdose 2 Severe systemic AEs were reported for 7.0% of participants Postdose 1 and by 4.1% of participants Postdose 2.
A total of 8 participants reported vaccine-related systemic AEs Postdose 1considered severe by the investigator: irritability (2), febrile convulsion (3), decreased appetite (1), pyrexia (2). Two participants reported vaccine-related systemic AEs Postdose 2 considered severe by the investigator: irritability (1), pyrexia (1). All of these events resolved without sequelae.

Vaccine-related Systemic Adverse Events
The proportions of participants who experienced vaccine-related systemic AEs from Days 1 to 42 Postdose 1 or Postdose 2 were comparable between the vaccination groups both Postdose 1 (23.1% in the PE34 group compared to 22.0% in the 2016 CP group) and Postdose 2 (10.1% in the PE34 group compared to 11.7% in the 2016 CP group). Overall, a higher proportion of participants experienced vaccine-related systemic AEs Postdose 1 (22.5%) compared to Postdose 2 (10.9%). The most commonly reported vaccine-related systemic AEs after each dose in both vaccination groups were pyrexia (7.5% overall Postdose 1 and 3.2% overall Postdose 2) and irritability (7.2% overall Postdose 1 and 3.8% overall Postdose 2).

The majority of vaccine-related systemic AEs were mild or moderate in intensity. Vaccine-related systemic AEs that were considered severe by the investigator were reported by 8 participants Postdose 1 (febrile convulsion [3 in the PE34 group], irritability [1 in the PE34 group and 1 in the CP 2016 group], pyrexia [1 in the PE 34 group and 1 in the CP 2016 group], rash vesicular [1 in the PE 34 group], decreased appetite [1 in the CP 2016 group]) and 2 participants Postdose 2 (irritability [1 in the CP 2016 group], pyrexia [1 in the CP 2016 group]). All of these events resolved without sequelae.

Fever
Daily temperatures were reported through Day 42 after each vaccination. All temperatures are summarized using the Brighton Collaborative cutpoints, which include the categories of temperatures <100.4° F (⩾38.0° C), and then ⩾100.4° F (⩾38.0° C) in 0.5° C increments.
Additionally, the incidence of elevated temperature (fever), defined as ⩾102.2° F (⩾39.0° C) oral equivalent, is reported.

The incidence of fever (temperature ⩾102.2° F [⩾39.0° C] oral equivalent) from Days 1 to 42 after each dose was comparable across all day ranges between the 2 vaccination groups. The incidence of fever was lower Postdose 2 compared with Postdose 1. Postdose 1, the highest rate of fever was observed from Days 1 to 14 Postdose 1 (specifically, between Days 6 to 14) [Table 26]. Postdose 2, the highest rate of fever was reported from Days 29 to 42 Postdose 2 [Table 27]. The distribution of maximum temperature reported from Days 1 to 42 after each dose was comparable for both vaccination groups for each temperature and day range.

Table 26 Analysis of Rate of Fever (Temperature ⩾ 102.2 ° F [39.0 ° C] Oral Equivalent) by Day Range Between Vaccination Groups – Days 1 to 42 Postdose 1

Day Range		VARIVAX™ PE34 + M-M-R™ II n %	VARIVAX™ (2016 CP) + M-M-R™ II n %	Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II	
				Estimate (95% CI)[†]	p-value[†]
Days 1 to 5	Subjects in population	299	300		
	Without temperature data (Days 1 to 5)[‡]	2	4		
	With temperature data (Days 1 to 5)	297	296		
	Maximum Temperature (Oral or Oral Equivalent)				

Day Range		VARIVAX™ PE34 + M-M-R™ II n	%	VARIVAX™ (2016 CP) + M-M-R™ II n	%	Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II Estimate (95% CI)†	p-value†
Days 1 to 5	≥102.2 °F [≥ 39.0 °C]	6	(2.0)	3	(1.0)	1.0 (-1.2, 3.4)	0.316
Days 6 to 14	Subjects in population	299		300			
	Without temperature data (Days 6 to 14)‡	8		5			
	With temperature data (Days 6 to 14)	291		295			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	13	(4.5)	15	(5.1)	-0.6 (-4.3, 3.0)	0.726
Days 15 to 28	Subjects in population	299		300			
	Without temperature data (Days 15 to 28)‡	9		9			
	With temperature data (Days 15 to 28)	290		291			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	11	(3.8)	10	(3.4)	0.4 (-2.9, 3.6)	0.818
Days 29 to 42	Subjects in population	299		300			
Days 29 to 42	Without temperature data (Days 29 to 42)‡	14		14			
	With temperature data (Days 29 to 42)	285		286			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	10	(3.5)	6	(2.1)	1.4 (-1.4, 4.5)	0.307

† Based on Miettinen & Nurminen method.
‡ Includes subjects whose temperature methods were unreported or unable to be converted to oral equivalent for the specific day range.
Multiple occurrences of maximum temperature are counted only once.
Non-oral temperatures have been converted to oral equivalent.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

Table 27 Analysis of Rate of Fever (Temperature ⩾ 102.2 ° F [39.0 ° C] Oral Equivalent) by Day Range Between Vaccination Groups – Days 1 to 42 Post-dose 2

Day Range		VARIVAX™ PE34 + M-M-R™ II n	%	VARIVAX™ (2016 CP) + M-M-R™ II n	%	Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II Estimate (95% CI)†	p-value†
Days 1 to 5	Subjects in population	276		282			
	Without temperature data (Days 1 to 5)‡	11		11			
	With temperature data (Days 1 to 5)	265		271			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	1	(0.4)	3	(1.1)	-0.7 (-2.9, 1.1)	0.327
Days 6 to 14	Subjects in population	276		282			
	Without temperature data (Days 6 to 14)‡	7		9			
	With temperature data (Days 6 to 14)	269		273			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	6	(2.2)	3	(1.1)	1.1 (-1.2, 3.8)	0.303
Days 15 to 28	Subjects in population	276		282			
	Without temperature data (Days 15 to 28)‡	11		7			
	With temperature data (Days 15 to 28)	265		275			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	8	(3.0)	6	(2.2)	0.8 (-2.1, 3.9)	0.541
Days 29 to 42	Subjects in population	276		282			

Days 29 to 42	Without temperature data (Days 29 to 42)‡	17		8			
	With temperature data (Days 29 to 42)	259		274			
	Maximum Temperature (Oral or Oral Equivalent)						
	≥102.2 °F [≥ 39.0 °C]	10	(3.9)	6	(2.2)	1.7 (-1.3, 5.0)	0.259

† Based on Miettinen & Nurminen method.
‡ Includes subjects whose temperature methods were unreported or unable to be converted to oral equivalent for the specific day range.
Multiple occurrences of maximum temperature are counted only once.
Non-oral temperatures have been converted to oral equivalent.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

CHMP comment
The rate of fever 39.0 °C postvaccination 1 was reported with a low frequency of 11.8 % (VARIVAX PE34+MMRVAXPRO-group) versus 9.8 % (VARIVAX 2016CP+MMRVAXPRO-group) and postvaccination 2 with a frequency of 8.9% versus 6.1 %, respectively. Overall the incidence of reported fever was low for concomitant administration of VARIVAX and MMRVAXPRO. The reporting rate of fever was comparable between both vaccination groups at all time points.

Vaccine-specific Rashes and Mumps-Like Symptoms
The incidence of vaccine-specific rashes reported from Days 1 to 42 Postdose 1 or Postdose 2 was low and comparable between the vaccination groups. The incidence of vaccine-specific rashes was generally higher Postdose 1 compared with Postdose 2, with the highest number observed during Days 6 to 14 Postdose 1. None of these rashes were SAEs. No participants in either vaccination group experienced mumps-like symptoms.

Serious Adverse Events

Few participants experienced SAEs during the study, whether during the:
• safety follow-up period from Days 1 to 42 Postdose 1 or Postdose 2 (4 participants in the PE34 group and 1 participant in the 2016 CP group); or
• extended safety follow-up period from Day 43 Postdose 2 to Day 180 Postdose 2 (2 participants in the PE34 group and 4 participants in the CP 2016 group).

A total of 6 participants (2%) in each vaccination group experienced SAEs during the study (Day 1 to Day 180 Postdose 2).
All SAEs, except 1 in each vaccination group, were in the Infections and infestations SOC [Table 28].
No SAEs were considered to be vaccine-related (to VARIVAX or M-M-R II) and none led to discontinuation of study vaccine, discontinuation from the study, or death.

Table 28 Analysis of Subjects With Serious Adverse Events by System Organ Class (Incidence > 0% in One or More Vaccination Groups) Day 1 Through End of Study (Days 180 Post-dose 2)

	VARIVAX™ PE34 + M-M-R™ II		VARIVAX™ (2016 CP) + M-M-R™ II		Difference in % vs VARIVAX™ (2016 CP) + M-M-R™ II
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population with follow-up	299		300		
with one or more Serious adverse events	6	(2.0)	6	(2.0)	0.0 (-2.5, 2.6)
with no Serious adverse events	293	(98.0)	294	(98.0)	-0.0 (-2.6, 2.5)
Infections and infestations	**5**	**(1.7)**	**6**	**(2.0)**	**-0.3 (-2.8, 2.1)**
Adenovirus infection	1	(0.3)	0	(0.0)	0.3 (-0.9, 1.9)
Arthritis bacterial	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Bronchiolitis	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Cellulitis	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Croup infectious	1	(0.3)	0	(0.0)	0.3 (-0.9, 1.9)
Enterovirus infection	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Gastroenteritis	1	(0.3)	1	(0.3)	0.0 (-1.6, 1.6)
Osteomyelitis	1	(0.3)	0	(0.0)	0.3 (-0.9, 1.9)
Pharyngeal abscess	1	(0.3)	0	(0.0)	0.3 (-0.9, 1.9)
Pneumonia	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Respiratory syncytial virus bronchiolitis	2	(0.7)	0	(0.0)	0.7 (-0.6, 2.4)
Nervous system disorders	**0**	**(0.0)**	**1**	**(0.3)**	**-0.3 (-1.9, 0.9)**
Febrile convulsion	0	(0.0)	1	(0.3)	-0.3 (-1.9, 0.9)
Reproductive system and breast disorders	**1**	**(0.3)**	**0**	**(0.0)**	**0.3 (-0.9, 1.9)**
Balanoposthitis	1	(0.3)	0	(0.0)	0.3 (-0.9, 1.9)

[†] Based on Miettinen & Nurminen method.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Post-marketing Summary

At the time of this submission, varicella virus vaccine live (Oka/Merck) has been registered and approved in more than 70 countries. There are no records of any registration being revoked or withdrawn for safety reasons.

Patient exposure estimates were calculated from the Company internal distribution data from the WFRS and FSA database. Patient exposure estimates from the WFRS and FSA were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods. Approximately 242,363,678 patients are estimated to have been vaccinated, based on the assumption that each patient received one dose, as displayed by region in [Table 29]. The estimated number of marketed varicella virus vaccine live (Oka/Merck) doses distributed worldwide since market introduction (17-MAR-1995) to 16-MAR-2019 is approximately 242,363,678 based on the available data and the assumption that each patient received one dose.

Table 29 Cumulative Post-authorization Exposure by Country/Region

Country/Region	Cumulative Postauthorization Exposure (17-Mar-1995 to 16-Mar-2019)	
	Distribution (Number of Doses)	Exposure (Number of Patients Vaccinated)[a]
US	181,360,491	181,360,491
Non-EU/Non-US	43,277,784	43,277,784
EU	17,725,403	17,725,403
Total	**242,363,678**	**242,363,678**

2.3.3. Discussion on clinical aspects

The study protocol for study V210 was designed to proof that the new production line (PE34) of VARIVAX and the current (2016 CP) were comparable and non-inferior regarding immunogenicity and safety.

With regards to immunogenicity all 3 primary endpoints were met. Non-inferiority was demonstrated based on the VZV antibody response rate, VZV antibody GMTs, and acceptable VZV antibody response rates at 6 weeks postdose 1 in the VARIVAX PE34 process group compared to those induced by VARIVAX (2016 CP) group. The pre-specified success criterions for these 3 hypotheses were met. Also, the secondary immunogenicity endpoint was met. The seroconversion rate was 100 % for both groups and the proportion of participants with VZV antibody titers at the threshold of ≥5 gpELISA units/mL at 6 weeks Postdose 1 was comparable between both dosing groups. The MAH also demonstrated that there was no specific gender influence regarding the immune response after one dose VARIVAX. Additionally, it was proven that the initially 71 seropositive subjects reached the threshold of ≥5 gpELISA units/mL at 6 weeks Postdose 1 comparable in both dosing groups and all subjects 100 % in the VARIVAX PE34 group. Immune response rate of M-M-RVAXPRO was not evaluated within this trial, which was co-administered with both groups of VARIVAX.

Collecting the safety data in trial V210 the evaluation showed that the proportion of participants with solicited injection site AES were comparable in both co-administration groups. With regards to systemic AEs including fever the reported frequencies were comparable in both dosing groups and the majority of AEs were of mild and moderate intensity. Severe systemic AEs were reported from 7 % of sujects Postdose 1 and from 4.1 % after Postdose 2. In general, the incidence of AEs including rashes was lower for participants Postdose 2 compared to Postdose 1.

Only 6 subjects per dosing group reported SAEs and all SAEs were considered as unrelated by the investigators.

The adverse events reported from clinical trial VARIVAX-V210 are consistent with the known safety profile of VARIVAX and M-M-RVAXPRO as described in the product information.

The immunogenicity and safety data collected during the trial about VARIVAX and M-M-RVAXPRO confirmed its positive benefit-risk balance in the approved indications.

M-M-RVAXPRO SmPC comments

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

…

Excipients with known effect:

The vaccine contains 14.5 mg of sorbitol. ~~See section 4.4.~~

For the full list of excipients, see section 6.1.

4.4 Special warnings and precautions for use

…

~~This vaccine contains 14.5 mg of sorbitol as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this vaccine.~~

CHMP comment

Within a future variation where PI will be changed the above-mentioned warning statement should be deleted according to the updated excipient guideline. According to the excipient guideline a warning statement should only be added when the medicine for parental use, other than IV, contains Sorbitol more than 5mg/kg/day and children in the age of 12 months are usually heavier than 3 kg.

3. CHMP overall conclusion and recommendation

VARIVAX PE34 vaccine induces an acceptable immune response that is non-inferior to that for VARIVAX (2016 CP).

The adverse events reported from clinical trial VARIVAX-V210 are consistent with the known safety profile of VARIVAX and M-M-RVAXPRO as described in the product information and were comparable between both VARIVAX production lines.

The immunogenicity and safety data collected during the trial about VARIVAX and M-M-RVAXPRO confirmed its positive benefit-risk balance in the approved indications.

☒ PAM Fulfilled:

No regulatory action required at present. Within a future variation affecting the M-M-RVAXPRO PI, the SmPC comments mentioned in the Assessment Report for this P46 038 procedure should be taken into consideration.