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Committee for Medicinal Products for Human Use (CHMP)

Assessment Report under Article 46

ProQuad

Measles, mumps, rubella and varicella vaccine, live

Procedure No. EMA/H/C/0622/P46/026

Note

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

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1. Assessment

Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of study MRV02C in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended and as part of follow up measure 026

Study MRV02C is an open-label randomised, comparative, multi-centre study to evaluate the immunogenicity and safety of a 2-dose regimen of ProQuad manufactured with rHA administered to healthy children from 9 months of age.

Please note that this study was already submitted for M-M-RVAXPRO in the context of variation II/024 to extend the age indication.

Assessment

Study MRV02C is an open-label, randomised, comparative, multi-centre study designed to demonstrate that a 2-dose regimen of ProQuad manufactured with rHA administered at a 3 month interval to different age groups of healthy children at the time of the first dose is non-inferior in terms of antibody response rates. The study was conducted in 3 countries (Finland, Germany, France) between November 2007 and December 2008.

In this phase 3b study, a total of 1,620 subjects were randomised in one of 3 groups (1:1:1; 540 subjects per group), to receive 2 doses of ProQuad manufactured with rHA at a 3-month interval. The same interval of time was to be respected between Dose 1 and Dose 2 of ProQuad in each group in order to solely evaluate the impact of the vaccination age on a unique vaccination pattern.

The schedule of vaccinations and blood sample collections is shown in Table 1. Blood samples were obtained from subjects just prior to ProQuad dose 1 vaccination (blood sample 1), 42 days (±14) after ProQuad dose 1 vaccination (blood sample 2), and 42 days (±14) after ProQuad dose 2 vaccination (blood sample 3).

Table 1: Vaccination Group Assignments and Blood Draws

	VISIT 1	**VISIT 2**	**VISIT 3**	**VISIT 4**	**VISIT 5**
Visit Intervals	**-**	**Day 0**	**Visit 2 + 42 days**	**Visit 2 + 90 days**	**Visit 4 + 42 days**
Time Windows	Visit 2 could be done at the same time as Visit 1 for Group 1		+ 14 days	+ 14 days	+ 14 days
Subject's age for Group 1	9 months	9 months			

	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5
Visit Intervals	**-**	**Day 0**	**Visit 2 + 42 days**	**Visit 2 + 90 days**	**Visit 4 + 42 days**
Subject's age for Group 2		11 months			
Subject's age for Group 3		12 months			
Blood samples (3mL)		Blood Sample 1	Blood Sample 2		Blood Sample 3
Vaccination		Dose 1		Dose 2	

Vaccine

ProQuad (manufactured with rHA) is a combined attenuated live virus vaccine for vaccination against measles, mumps, rubella and varicella viruses. It is a lyophilised vaccine powder and solvent for suspension for injection and stored in separate vials at 2°C-8°C.

Study objectives

The objectives of study MRV02C were as follows:

- The *first primary objective* was to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age at the time of Dose 1 is as immunogenic as in healthy children of 12 months of age at the time of Dose 1, in terms of antibody response rates to measles, mumps, rubella and varicella at Day 42 following Dose 2.
- The *second primary objective*, which was to be evaluated only if the first primary objective was reached, was to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 9 months of age at the time of Dose 1 is as immunogenic as in healthy children of 12 months of age at the time of Dose 1, in terms of antibody response rates to measles, mumps, rubella and to varicella at Day 42 following Dose 2.
- The *third primary objective* was to demonstrate that a 2-dose regimen of ProQuad administered at a 3-month interval to healthy children of 11 months of age and 9 months of age at the time of Dose 1 is well tolerated compared to healthy children of 12 months of age at the time of Dose 1.
- The *secondary immunogenicity objectives* were to describe the antibody titres to measles, mumps, rubella and varicella at Day 42 following Dose 1 and Dose 2 of ProQuad administered to healthy children from 9 months of age.
- The *secondary safety objectives* were to evaluate the safety profile of Dose 1 and Dose 2 of ProQuad administered to healthy children from 9 months of age.

The primary endpoints for immunogenicity were the antibody response rates, which were defined as:

- Measles antibody titre >=255 mIU/ml in subjects with baseline titre <255 mIU/ml.
- Mumps antibody titre >=10 ELISA Ab units/ml in subjects with baseline titre <10 ELISA Ab units/ml.
- Rubella antibody titre >=10 IU/ml in subjects with baseline titre <10 IU/ml.
- Varicella antibody titre >=5 gpELISA units/ml

Serology Assays

The serology assays were conducted at Merck Research Laboratories (MRL) and PPD, Vaccines and Biologics, U.S.A.

Antibodies to measles, mumps and rubella were determined by validated enzyme-linked immunosorbent assays (ELISA) and antibodies to varicella were determined by glycoprotein enzyme-linked immunosorbent assay (gpELISA).

The serostatus cut-off of the measles ELISA was 255 mIU/ml. The basis for the cut-off was a review of the literature in which the calculated result for the seroprotective antibody level expressed in mIU/ml (when compared to the World Health Organization reference standard) was reported as 255 mIU/ml.

The serostatus cut-off used for the mumps ELISA was determined as the lowest antibody concentration that was distinguishable from a panel of 72 ‚negative' samples.

For rubella the serostatus cut-off for the assay was based on the WHO standard.

The cut-off used in the varicella gpELISA assay was internally defined as 1.25 gpELISA units/ml.

Statistical methods

The **Full Analysis Set** (FAS) consisted of all randomised subjects who received at least one dose of the study vaccine and with any post vaccination immunogenicity evaluation.

The **Per Protocol Set** (PPS) was defined as all randomised subjects excluding subjects with protocol violations which may interfere with the immunogenicity evaluation.

Two subsets of the Per Protocol Set were defined for the immunogenicity evaluation at the corresponding time point, *i.e.*:

- **PPS1** consisted of all randomised subjects excluding subjects with protocol violation(s) which may interfere with the immunogenicity evaluation post-Dose 1.

  PPS2 consisted of all randomised subjects excluding subjects with protocol violation(s) which may interfere with the immunogenicity evaluation post-Dose 2.

Analysis of the immunogenicity

The immunogenicity analysis of the primary criteria was performed on the PPS in initially seronegative subjects (main analysis) and on the FAS (supportive analysis).

For the Per Protocol analysis, only initially seronegative subjects were included in the analyses of the corresponding valence:

- For measles, subjects with baseline (BS1) measles antibody titres <255 mIU/mL (i.e. initially seronegative to measles),
- For mumps, subjects
- with baseline (BS1) mumps antibody titres <10.0 ELISA Ab units/mL (i.e. initially seronegative to mumps),
- For rubella, subjects with baseline (BS1) rubella antibody titres <10.0 IU/mL (i.e. initially seronegative to rubella),
- For varicella, subjects with baseline (BS1) varicella antibody titres <1.25 gpELISA units/mL (i.e. initially seronegative to varicella).

The immunogenicity analysis of the secondary criteria was performed on both PPS in initially seronegative subjects and FAS. Also, descriptive statistics were provided on initially seropositive subjects at inclusion, if seropositive subjects represent at least 5% of the FAS.

All subjects with serology results following Dose 2 of ProQuad were included in the FAS whatever antibody titres at baseline (BS1).

In relation with the first primary hypothesis, the estimates of the between groups differences in response rates (Group 2 - Group 3) were calculated together with their two-sided 95% CI. If the lower bounds of the CI were greater than –5% for measles, mumps and rubella response rates and greater than -10% for varicella response rate, it was concluded that the Group 2 response rates are non-inferior to the Group 3 response rates.

If the first primary objective was reached, the second primary hypothesis was tested. The estimates of the between groups differences in response rates (Group 1 - Group 3) were calculated together with their two-sided 95% CI. If the lower bounds of the CI were greater than –5% for measles, mumps and rubella response rates and greater than -10% for varicella response rate, it was concluded that the Group 1 response rates are non-inferior to the Group 3 response rates.

Assessor's comment: The non-inferiority margins were appropriately defined.

Results

Disposition of subjects

A total of 1,626 subjects were enrolled between 29 November 2007 and 14 April 2008. Six subjects were not randomised either due to protocol deviation or due to other reasons.

Randomised subjects were enrolled in three countries: 1,290 subjects (79.6%) into 15 centres in Finland, 140 subjects (8.6%) into 14 centres in France, and 190 subjects (11.7%) into 19 centres in Germany.

A total of 161 subjects (9.9%) were withdrawn from the study. The majority of subjects (137; 8.5%) were withdrawn before first vaccination, 18 subjects (1.1%) between first and second vaccination and six subjects (0.4%) after receiving the second vaccine dose. Given the differences in time between randomisation and first vaccination in the 3 groups, and taken into account in the determination of the

sample size, the number of subjects withdrew from the study before Dose 1 was higher in Group 2 (first dose at 11 months) and Group 3 (first dose at 12 months), 10.4% and 12.8% of subjects respectively, than in Group 1 (first dose at 9 months), 2.2% of subjects.

The main reason for withdrawal was for personal reason but 3 subjects were withdrawn for adverse event: 1 subject (15073) from Group 3 before Dose 1 (viral infection), and 2 subjects from Group 1 after Dose 1 due to serious adverse events assessed by the investigator as non-related to study vaccine (subject 05100 for convulsion 2 months after vaccination and subject 15027 for gastroenteritis rotavirus).

The Full Analysis Set consisted of 1,473 subjects (90.9%): 527 subjects in Group 1, 480 subjects in Group 2 and 466 subjects in Group 3.

The PPS consisted of 1,446 subjects (89.3%) and the PPS1 consisted of 1,426 subjects (88.0%) including 519 subjects in Group 1, 460 subjects in Group 2 and 447 subjects in Group 3.

Demographic and other baseline characteristics were comparable between groups except for gender: Groups 1 and 2 were constituted of 48% of boys and 52% of girls whereas in Group 3, the gender distribution was 52% of boys and 48% of girls. Overall, mean (+/-standard deviation [SD]) age at inclusion was 9.48 (+/-0.30) months, mean weight was 9.22 (+/-1.14) kg, and mean height was 72.96 (+/-2.64) cm.

At first vaccination, mean (+/- SD) age was 9.51 months (+/-0.30) in Group 1, 11.26 months (+/-0.23) in Group 2, and 12.32 months (+/-0.24) in Group 3.

Regarding the serostatus at baseline, the percentage of subjects considered seropositive for measles, mumps and rubella at the time of first vaccination was comparable in the 3 groups (Table 2). For varicella the percentage of seropositive subjects decreased with increasing age indicating the persistence of maternal antibodies.

Table 2: Serostatus at the time of Dose 1 - FAS

	Group 1	**Group 2**	**Group 3**
	9 months	**11 months**	**12 months**
	(N=527)	**(N=480)**	**(N=466)**
Measles ≥255 mIU/mL	11 (2.1%)	7 (1.5%)	9 (1.9%)
Mumps ≥10 Elisa Ab units/mL	20 (3.8%)	10 (2.1%)	30 (6.5%)
Rubella ≥10 IU/mL	1 (0.2%)	0	0
Varicella ≥1.25 gpELISA units/mL	295 (56.0%)	150 (31.3%)	90 (19.4%)
Percentage are calculated based on the number of subjects of the Full Analysis Set with results available at baseline: Group 1: 527 subjects, Group 2: 479 subjects and Group 3: 465 subjects			

Immunogenicity results

First primary objective: immunogenicity after the second dose of ProQuad when first dose was given at 11 months (Group 2) compared to 12 months (Group 3)

For both Group 2 and Group 3 the response rates after the second dose of ProQuad were ≥98.0% for measles, mumps, and rubella in the antigen-specific PPS (Table 3).

Table 3: Antibody Response Rates to Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad – Antigen-specific PPS

	Group 2 11 months			Group 3 12 months		
	N	Number of responders (Response rate)	[95% CI]	N	Number of responders (Response rate)	[95% CI]
Measles	440	431 (98.0%)	[96.2;99.1]	434	429 (98.8%)	[97.3;99.6]
Mumps	436	434 (99.5%)	[98.4;99.9]	414	412 (99.5%)	[98.3;99.9]
Rubella	445	442 (99.3%)	[98.0;99.9]	443	441 (99.5%)	[98.4;99.9]
Varicella	299	299 (100%)	[98.8;100]	347	347 (100%)	[98.9;100]

The first primary immunogenicity hypothesis of the non-inferiority of Group 2 compared to Group 3 was met for measles, mumps, rubella and varicella (Table 4).

Table 4: Non-inferiority Analysis (with Stratification by Country) for Response Rates to

Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad for Group 2 (First Dose at 11 Months) Compared to Group 3 (First Dose at 12 Months) – Antigen-specific PPS

	Estimate of the difference	[95% CI]	Non-Inferiority (a)
Measles Response rate Group 2 – Group 3	-0.91%	[-2.82;0.87]	Yes
Mumps Response rate Group 2 – Group 3	0.03%	[-1.20;1.32]	Yes
Rubella Response rate Group 2 – Group 3	-0.22%	[-1.55;1.03]	Yes
Varicella Response rate Group 2 – Group 3	0.00%	[-1.28;1.10]	Yes

Second primary objective: immunogenicity after the second dose of ProQuad when first dose was given at 9 months (Group 1) compared to 12 months (Group 3)

For both Group 1 (first dose at 9 months) and Group 3 (first dose at 12 months) the response rates after the second dose of ProQuad were ≥99.2% for mumps, rubella and varicella in the antigen-specific PPS. For measles, the response rate was 94.9% in Group 1 and 98.8% in Group 3 (Table 5).

Table 5: Antibody Response Rates to Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad – Antigen-specific PPS

	Group 1 9 months			Group 3 12 months		
	N	Number of responders (Response rate)	[95% CI]	N	Number of responders (Response rate)	[95% CI]
Measles	490	465 (94.9%)	[92.6;96.7]	434	429 (98.8%)	[97.3;99.6]
Mumps	481	477 (99.2%)	[97.9;99.8]	414	412 (99.5%)	[98.3;99.9]
Rubella	500	497 (99.4%)	[98.3;99.9]	443	441 (99.5%)	[98.4;99.9]
Varicella	208	208 (100%)	[98.2;100]	347	347 (100%)	[98.9;100]

The second primary immunogenicity hypothesis of the non-inferiority of Group 1 compared to Group 3 was met (main analysis, stratified by country) for mumps, rubella and varicella but not for measles (Table 6).

Table 6: Non-inferiority Analysis (with Stratification by Country) for Antibody Response Rates to

Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad for Group 1

(First Dose at 9 Months) Compared to Group 3 (First Dose at 12 Months) – Antigen-specific PPS

	Estimate of the difference	[95% CI]	Non-Inferiority (a)
Measles Response rate Group 1 – Group 3	-3.97%	[-6.44;-1.87]	No
Mumps Response rate Group 1 – Group 3	-0.35%	[-1.71;1.01]	Yes
Rubella Response rate Group 1 – Group 3	-0.15%	[-1.34;1.09]	Yes
Varicella Response rate Group 1 – Group 3	0.00%	[-1.83;1.10]	Yes
(a) Non-inferiority is achieved since the lower bound of the two-sided 95% confidence interval (CI) is above -5% for measles, mumps, and rubella and above -10% for varicella.			

Assessor's comment: The data clearly demonstrate that vaccination of infants 9 months of age results in lower response rates to the measles component. This observation is most likely due to circulating maternal antibodies or the immaturity of the immune system of the children. These results confirm that a further dose of vaccine should be given later on as catch-up to ensure high seroprotection rates against measles.

Secondary objective: Response rates for measles, mumps, rubella and varicella following Dose 1 and 2

Response rates for measles, mumps, rubella and varicella at 6 weeks post-Dose 1 and Dose 2 on antigen specific PPS initially seronegative subjects are summarized in Table 7.

The response rates reported for the FAS population are in the same magnitude for all three groups and were comparable.

Table 7: Antibody Response Rate to Measles, Mumps, Rubella and Varicella 6 Weeks Post-Dose 1 and Post-Dose 2 of ProQuad– Antigen Specific PPS in initially seronegative subjects

		Group 1 9 months		Group 2 11 months		Group 3 12 months	
		N	n (response rate) [95% CI]	N	n (response rate) [95% CI]	N	n (response rate) [95% CI]
Measles	**Post-Dose 1**	508	369 (72.6%) [68.5; 76.5]	455	400 (87.9%) [84.6; 90.8]	438	395 (90.2%) [87.0; 92.8]
	Post-Dose 2	490	465 (94.9%) [92.6; 96.7]	440	431 (98.0%) [96.2; 99.1]	434	429 (98.8%) [97.3; 99.6]
Mumps	**Post-Dose 1**	499	482 (96.6%) [94.6; 98.0]	453	447 (98.7%) [97.1; 99.5]	417	410 (98.3%) [96.6; 99.3]
	Post-Dose 2	481	477 (99.2%) [97.9; 99.8]	436	434 (99.5%) [98.4; 99.9]	414	412 (99.5%) [98.3; 99.9]
Rubella	**Post-Dose 1**	518	506 (97.7%) [96.0; 98.8]	460	455 (98.9%) [97.5; 99.6]	447	438 (98.0%) [96.2; 99.1]
	Post-Dose 2	500	497 (99.4%) [98.3; 99.9]	445	442 (99.3%) [98.0; 99.9]	443	441 (99.5%) [98.4; 99.9]
Varicella	**Post-Dose 1**	220	209 (95.0%) [91.2; 97.5]	312	305 (97.8%) [95.4; 99.1]	353	344 (97.5%) [95.2; 98.8]
	Post-Dose 2	208	208 (100%) [98.2; 100]	299	299 (100%) [98.8; 100]	347	347 (100%) [98.9; 100]

Secondary objective: Measles, mumps, rubella and varicella GMT following Dose 1 and 2

A summary of the mean antibody titres to measles, mumps, rubella and varicella 6 weeks after the first and second dose of ProQuad on antigen specific PPS initially seronegative subjects is given in Table 8.

The GMTs reported for the FAS population are in the same magnitude for all three groups and were comparable.

Table 8: Antibody Titres (GMT) to Measles, Mumps, Rubella and Varicella 6 Weeks after the First Dose and 6 Weeks after the Second Dose of ProQuad – Antigen Specific PPS in initially seronegative subjects

		Group 1 9 months		Group 2 11 months		Group 3 12 months	
		N	GMT [95% CI]	N	GMT [95% CI]	N	GMT [95% CI]
Measles (mIU/mL)	**Post-Dose 1**	508	942 [808;1098]	455	1977 [1736;2252]	438	2500 [2199;2841]
	Post-Dose 2	490	1817 [1645;2006]	440	2320 [2129;2529]	434	2703 [2492;2933]
Mumps (ELISA Ab units/mL)	**Post-Dose 1**	499	73 [68;79]	453	91 [84;99]	417	86 [79;93]
	Post-Dose 2	481	157 [147;168]	436	163 [151;175]	414	172 [159;185]
Rubella (IU/mL)	**Post-Dose 1**	518	64 [60;70]	460	77 [71;83]	447	81 [75;88]
	Post-Dose 2	500	106 [99;113]	445	116 [109;124]	443	118 [111;126]
Varicella (gpELISA units/mL)	**Post-Dose 1**	220	15 [13;16]	312	15 [14;16]	353	15 [14;16]
	Post-Dose 2	208	431 [372;500]	299	460 [410;517]	347	515 [466;569]

Assessor's comment: For measles, a significant difference in the response rates and GMTs in baseline seronegative children is observed depending on the age of administration of the vaccine dose. Moreover the increase in antibody titers post dose 2 was highest in the youngest age category compared to Group 2 and 3. In group 1, an increase from 942 mIU/ml after the first dose to 1817 mIU/ml after the second dose was observed, which is still lower than the GMT reported after the first dose in older infants. This low response might be due to interfering low circulating maternal antibodies or the immaturity of the immune system.

In summary the post dose 1 and 2 responses are significantly lower in children 9 months of age than in infants 11 or 12 months of age. These results corroborate the necessity of further vaccine doses, when children are vaccinated in their first year of life against measles. Clear advice on the administration of further doses should be provided in section 4.2 of the SmPC.

Antibody response in initially seropostive subjects

Response rates and geometric means of measles, mumps, and rubella antibody titres at 6 weeks post-Dose 1 and post-Dose 2 on antigen specific FAS in initially seropositive subjects were presented in the CSR. As regards measles 11 subjects in group 1 were found to be seropositive prior vaccination (≥255mUI/ml). Following vaccination a very heterogeneous immune response against measles was observed within and across the different groups (see below Table 9).

Table 9: Summary of measles antibody response in initially measles seropositive subjects

		Group 1 9 months		Group 2 11 months		Group 3 12 months	
		N	**n (response rate) [95% CI]**	**N**	**n (response rate) [95% CI]**	**N**	**n (response rate) [95% CI]**
Response rates	**Day 0**	11	11 (100%) [71.5;100.0]	7	7 (100%) [59.0;100.0]	9	9 (100%) [66.4;100.0]
	Post-Dose 1	11	7 (63.6%) [30.8;89.1]	7	6 (85.7%) [42.1;99.6]	9	9 (100%) [66.4;100.0]
	Post-Dose 2	11	9 (81.8%) [48.2;97.7]	7	7 (100%) [59.0;100.0]	9	9 (100%) [66.4;100.0]
		N	**GMT [95% CI]**	**N**	**GMT [95% CI]**	**N**	**GMT [95% CI]**
Measles GMT in mIU/ml	**Day 0**	11	560 [291;1078]	7	307 [257;367]	9	457 [319;656]
	Post-Dose 1	11	1068 [255;4480]	7	2191 [487;9868]	9	3624 [1695;7748]
	Post-Dose 2	11	1164 [343;3950]	7	3531 [1653;7542]	9	2752 [1095;6917]
		N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
≥4-fold increase in titer compared to Day 0	**Post-Dose 1**	11	4 (36.4%)	7	6 (85.7%)	9	8 (88.9%)
	Post-Dose 2	11	3 (27.3%)	7	6 (85.7%)	9	6 (66.7%)

Assessor's comment: All subjects in group 2 and 3, who were seropositive for measles (titre >255 mIU/ml) prior vaccination had also a measles antibody titre >255 mIU/ml post dose 2. Only 81.9% of infants 9 months of age however were determined to have seroprotective antibody titers post dose 2. Although the number of subjects in this subgroup analysis is very low these results suggest interference of maternal antibodies on the immune response to measles vaccination.

Clinical safety

The Safety Set was defined as all subjects who received at least one dose of the study vaccine and who had safety follow-up data. Subjects were analysed according to *their real age at Dose 1*. Subjects with an age outside group definitions were reallocated to the group with a closer age definition.

Safety Measurements

The schedule for the evaluation of safety parameters is given below in Table 10.

Table 10: Schedule of Safety Parameters

<table>
<tr><td rowspan="6">Visit 1</td><td>Visit 2</td><td>-</td><td>-</td><td>Visit 4</td><td>-</td><td>-</td><td>Visit 5</td></tr>
<tr><td>Dose 1</td><td>Day 4
post-Dose 1</td><td>Day 28
post-Dose 1</td><td>Dose 2</td><td>Day 4
post-Dose 2</td><td>Day 28
post-Dose 2</td><td>Day 42 to 56 post-Dose 2</td></tr>
<tr><td colspan="2">Solicited injection-site adverse reactions</td><td></td><td colspan="2">Solicited injection-site adverse reactions</td><td></td><td rowspan="4"></td></tr>
<tr><td colspan="3">Rashes
Mumps-like symptoms</td><td colspan="3">Rashes
Mumps-like symptoms</td></tr>
<tr><td colspan="3">Unsolicited injection-site adverse reactions
Other systemic adverse events</td><td colspan="3">Unsolicited injection-site adverse reactions
Other systemic adverse events</td></tr>
<tr><td colspan="3">Temperature</td><td colspan="3">Temperature</td></tr>
<tr><td colspan="8">Serious adverse events</td></tr>
</table>

Patient exposure

The Safety Set consisted of 1,483 subjects (91.5%). One subject randomised in Group 2 (subject 12016) was over 12 months of age at Dose 1; this subject was analysed in Group 3 for safety analyses (according to real age at Dose 1). The extent of exposure is summarised in Table 11.

Table 11: Overall extent of exposure

	Group 1 9 months (N=541)	**Group 2 11 months (N=540)**	**Group 3 12 months (N=539)**	**Total (N=1620)**
Safety Set	529 (97.8%)	484 (89.6%)	470 (87.2%)	1483 (91.5%)

The median follow-up duration was 142 days (range 1; 189) in Group 1, 195 days (range 1; 255) in Group 2 and 225 days (range 1; 274) in Group 3.

Adverse events

Post dose 1:

In total, 81.3% of subjects in Group 1, 81.9% in Group 2 and 81.1% in Group 3 reported at least one injection-site adverse reaction or systemic adverse event within 28 days following Dose 1. Most of these subjects experienced at least one adverse event related to the study vaccine (injection-site adverse reaction or vaccine-related systemic adverse event): 58.7% of subjects in Group 1, 60.8% in Group 2 and 63.9% in Group 3.

Regarding fever, 8.8%, 10.3% and 14.8% of subjects reported rectal temperature ≥39.4°C in Groups 1, 2 and 3, respectively following the first dose of ProQuad, i.e. statistically more in Group 3 (first injection at 12 months) compared to Group 1 (first injection at 9 months) and Group 2 (first injection at 11 months).

Post dose 2:

In total, 72.5% of subjects in Group 1, 75.7% in Group 2 and 72.7% in Group 3 reported at least one injection-site adverse reaction or systemic adverse event within 28 days following Dose 2. Most of these subjects experienced at least one adverse event related to the study vaccine (injection-site adverse reaction or vaccine-related systemic adverse event): 55.0% of subjects in Group 1, 57.8% in Group 2 and 54.8% in Group 3.

As regards the occurrence of fever comparable number of subjects reported rectal temperature ≥39.4°C in the three groups following the second dose.

In summary the incidence and intensity of injection-site adverse reactions from Day 0 to Day 28 post-dose 1 and post dose 2 was comparable between groups.

Serious adverse events and deaths

Before the first administration of ProQuad, no serious adverse event was reported in Group 1, 1 serious adverse event was reported by 1 subject (0.2%) in Group 2 (gastroenteritis rotavirus), and 10 serious adverse events were reported by 7 subjects (1.5%) in Group 3 (bronchitis, gastroenteritis, laryngitis and concussion were reported by 1 subject each and gastroenteritis rotavirus, otitis media and tonsillitis were reported by 2 subjects each).

Serious adverse events occurring between the Dose 1 and 2 of ProQuad were more frequently reported by subjects from Group 1 (3.4%) than those from Group 2 and Group 3 (1.7% in each group). Serious adverse events included cardiac disorders, infections and infestations (mainly gastroenteritis rotavirus, gastroenteritis and bronchitis), injury, poisoning and procedural complications, nervous system disorders, respiratory, thoracic and mediastinal disorders and skin and subcutaneous tissue disorders. No serious adverse event occurring between Dose 1 and 2 or reported after the second dose were assessed by neither the investigator nor the sponsor to be related to the study vaccine.

No death was reported during the course of the study.

Assessor's comment: The safety profile is comparable across the different age groups following the first and second vaccination with ProQuad, indicating that in principle no safety concern is anticipated by vaccinating children from 9 months of age onwards.

2. Rapporteur's Overall Conclusion And further action if required

The immunogenicity data from study MRV02C investigating a 2-dose regimen of ProQuad (MMRV with rHA) in different age groups support the extension of the age indication to children from 9 months of age onwards under special circumstances, i.e. outbreak control. The data clearly indicate however that vaccination of infants at 9 months of age results in lower antibody responses especially as regards measles. The lower antibody responses are most likely due to interfering pre-existing maternal antibodies or the immaturity of the immune response of these children. Therefore additional vaccine doses are warranted later on in life. However no information on the effect of an additional dose of a measles containing vaccine to the primary immunisation course of ProQuad is currently available. As regards safety the incidence and intensity of adverse reactions was comparable in infants 9 months of age with infants 12 months of age.

Since it is favourable that measles containing vaccines are available for children from 9 months of age onwards to be used under special circumstances e.g. outbreak control, the MAH is asked to update the product information in that respect. It should however be made clear that the extended use has to follow official national recommendations.

Please note that the results of this study were already considered to extend the age indication of M-M-RVAXPRO (variation II/024).

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Overall Conclusion:

☒ PAC fulfilled (all commitments fulfilled) but further action required

☐ PAC not fulfilled (not all commitments fulfilled) and further action required:

As outcome of this assessment, the MAH is requested to update the Product Information as follows and to submit the corresponding variation by Q3/2010.

Extend of the age indication to children from 9 months of age under special circumstances.