15 March 2012
EMA/164243/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ProQuad

Measles, mumps, rubella and varicella vaccine (live)

Procedure No.: EMEA/H/C/000622/II/0055

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur MSD, SNC submitted to the European Medicines Agency on 8 December 2011 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
ProQuad	measles, mumps, rubella and varicella vaccine (live)	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include use from 9 months of age onwards under special circumstances.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Jan Mueller-Berghaus

1.2. Steps taken for the assessment

Submission date:	8 December 2011
Start of procedure:	18 December 2011
Rapporteurs' preliminary joint assessment report circulated on:	08 February 2012
Rapporteurs' updated joint assessment report circulated on:	9 March 2012
CHMP opinion:	15 March 2012

Information on Paediatric requirements

Not applicable

2. Scientific discussion

2.1. Introduction

ProQuad is a live attenuated vaccine, for the prevention of measles, mumps, rubella and varicella. The vaccine is indicated for immunisation of individuals from 12 months of age.

The refrigerator stable formulation of ProQuad was first authorised in the USA on 04 August 2006 and in Europe on 12 September 2006.

The Marketing Authorisation was renewed in 2011.

This variation was submitted following the CHMP assessment of Follow Up Measure P46-026 (CSR of the study MRV02C investigating a 2-dose regimen of ProQuad (MMRV with rHA) in different age groups supports the extension of the age indication to children from 9 months of age onwards under special circumstances, i.e. outbreak control), which has been submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

2.2. Clinical Efficacy aspects

Currently, ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in individuals from 12 months of age.

In some European countries, the current official recommendations for measles, mumps and rubella vaccination are below 12 months of age. In France for instance, it is recommended to administer the measles, mumps and rubella vaccines from 9 months of age for children who attend day care centres. In Germany, the standing vaccination committee (STIKO) recommends measles, mumps, rubella and varicella vaccination from 11 months of age. Moreover, WHO recommends vaccinating children from 9 months of age against measles. Consequently, the MAH performed study MRV02C with ProQuad to evaluate the safety and immunogenicity of a 2-dose regimen when the first dose is administered from 9 months of age. Study MRV02C is an open-label, randomised, comparative, multi-centre study designed to demonstrate that a 2-dose regimen of ProQuad manufactured with recombinant human albumin (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.

2.2.1. Methods – analysis of data submitted

Study Design

In this 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. Group 1 received the first dose of the vaccine at 9 months, Group 2 at 11 months, and Group 3 at 12 months of age.

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 number	**Visit 1(a)**	**Visit 2(a)**	**Visit 3**	**Visit 4**	**Visit 5**
Timelines		Day 0	Visit 2 + 42 days	Visit 2 + 90 days	Visit 4 + 42 days
Time windows			+ 14 days	+ 14 days	+ 14 days
Age of the subjects in **Group 1**	**9 months (randomisation into 1 of the 3 groups)**	**~9 months**	-	**~12 months**	-
Age of the subjects in **Group 2**		**~11 months**	-	**~14 months**	-
Age of the subjects in **Group 3**		**~12 months**	-	**~15 months**	-
Blood sampling		Blood Sample 1	Blood Sample 2	-	Blood Sample 3
Vaccinations		Dose 1	-	Dose 2	-

(a) For Group 1: Visit 1 and Visit 2 could be pooled and performed at the same time.

Vaccine

In the manufacturing of the doses of ProQuad used in this study MRV02C, human serum albumin (HSA) was replaced by recombinant human albumin (rHA).

The clinical ProQuad batch manufactured with rHA was considered representative for the licensed refrigerator-stable vaccine formulation, which is currently manufactured with HSA.

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 in subjects with baseline titre <1.25 gpELISA units/mL

Serology Assays

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.

2.2.2. Results

Subject Disposition

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, 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: one subject from Group 3 before Dose 1 (viral infection), and two subjects from Group 1 after Dose 1 due to serious adverse events assessed by the investigator as non-related to study vaccine (one subject for convulsion 2 months after vaccination and one subject 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 characteristics

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 mIU/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, rubella and varicella 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
(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.			

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.			

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 titres following Dose 1 and 2

A summary of the geometric mean antibody titres (GMTs) 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]

Antibody response in initially seropositive 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 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%)

2.2.3. Discussion

Concerning the study design, the CHMP agreed that the non-inferiority margins were appropriately defined for this study. The immune responses against mumps, rubella and varicella were comparable between the groups, and for the second primary objective, non-inferiority was reached between Group 1 (1st dose at 9 months) and Group 3 (1st dose at 12 monts of age). However, 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 titres 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 to 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. Section 4.2 of the SmPC was therefore revised to provide clear advice on the administration of further doses.

In view of initially seropositive subjects, all subjects in group 2 and 3 who were seropositive for measles (titre >255 mUI/ml) prior to vaccination had also a measles antibody titre >255 mUI/ml post dose 2. Only 81.8% 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.

The CHMP considered that the data clearly demonstrate lower response rates to the measles component after vaccination of infants 9 months of age. This observation was considered to be likely due to circulating maternal antibodies or to 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 for this population.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

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.

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>

2.3.2. Results

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%)	483 (89.6%)	471 (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 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.

Injection site adverse reactions

The percentage of subjects reporting injection-site adverse reactions from Day 0 to Day 28 post dose

1 and 2 was comparable between groups (Table 12). Intensity of injection-site adverse reactions from Day 0 to Day 28 post-dose 1 and 2 was comparable between groups, being mainly of mild intensity or with a diameter <2.5 cm in each group.

Table 12: Injection-site adverse reactions from Day 0 to Day 28 after first and second dose

	Group 1 Dose 1 at 9 months n (%)		Group 2 Dose 1 at 11 months n (%)		Group 3 Dose 1 at 12 months (N=466) n (%)	
	Post-Dose 1 (N=528)	Post-Dose 2 (N=524)	Post-Dose 1 (N=480)	Post-Dose 2 (N=474)	Post-Dose 1 (N=466)	Post-Dose 2 (N=462)
Injection-site adverse reactions from Day 0 to Day 28	**216(40.9)**	**230(43.9)**	**193(40.2)**	**215(45.4)**	**190(40.8)**	**204(44.2)**
Solicited injection-site adverse reactions from Day 0 to Day 4	**115(21.8)**	**226(43.1)**	**112(23.3)**	**212(44.7)**	**129(27.7)**	**204(44.2)**
Injection site erythema	76(14.4)	214(40.8)	74(15.4)	193(40.7)	80(17.2)	180(39.0)
Injection site pain	60(11.4)	65(12.4)	50(10.4)	70(14.8)	64(13.7)	72(15.6)
Injection site swelling	12(2.3)	86(16.4)	22(4.6)	58(12.2)	11(2.4)	67(14.5)
Unsolicited injection-site adverse reactions from Day 0 to Day 28	**131(24.8)**	**10(1.9)**	**112(23.3)**	**21(4.4)**	**89(19.1)**	**18(3.9)**
Injection site bruising	7(1.3)	2(0.4)	6(1.3)	5(1.1)	5(1.1)	3(0.6)
Injection site eczema	1(0.2)	0	1(0.2)	0	0	1(0.2)
Injection site erythema (1)	88(16.7)	3(0.6)	79(16.5)	2(0.4)	61(13.1)	0
Injection site haematoma	7(1.3)	2(0.4)	2(0.4)	1(0.2)	7(1.5)	1(0.2)
Injection site haemorrhage	9(1.7)	1(0.2)	6(1.3)	5(1.1)	8(1.7)	3(0.6)
Injection site induration	6(1.1)	1(0.2)	2(0.4)	1(0.2)	3(0.6)	2(0.4)
Injection site irritation	0	0	2(0.4)	0	0	1(0.2)
Injection site movement impairment	0	0	0	0	0	1(0.2)
Injection site mass	0	0	1(0.2)	0	0	0
Injection site nodule	1(0.2)	0	1(0.2)	0	0	0
Injection site pain (1)	1(0.2)	0	2(0.4)	0	1(0.2)	0
Injection site papule	4(0.8)	0	1(0.2)	0	0	2(0.4)
Injection site pruritus	1(0.2)	0	0	0	0	0
Injection site rash	14(2.7)	2(0.4)	19(0.4)	4(0.8)	12(2.6)	3(0.6)
Injection site swelling (1)	19(3.6)	0	20(4.2)	0	13(2.8)	1(0.2)
Injection site urticaria	0	0	1(0.2)	2(0.4)	1(0.2)	0
Injection site vesicles	4(0.8)	0	0	1(0.2)	3(0.6)	0
Injection site warmth	0	0	0	0	1(0.2)	1(0.2)

n (%): number (percentage) of subjects presenting at least once the considered event
(1) with onset from Day 5 to Day 28

The most frequently reported unsolicited injection-site adverse reactions post dose 1 were injection-site erythema, swelling and rash.

Systemic adverse events

The percentage of subjects reporting systemic adverse events from Day 0 to Day 28 post-dose 1 was comparable between groups (Table 13). Among these subjects, 36.9% in Group 1, 37.9% in Group 2 and 41.8% in Group 3 experienced systemic adverse events related to ProQuad.

Table 13: Systemic adverse events from Day 0 to Day 28 **post dose 1** (with an incidence >1% for vaccine-related AE)

	Group 1 Dose 1 at 9 months (N=528)		Group 2 Dose 1 at 11 months (N=480)		Group 3 Dose 1 at 12 months (N=466)	
	All	Related to ProQuad	All	Related to ProQuad	All	Related to ProQuad
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Systemic adverse event from Day 0 to Day 28	**380 (72.0%)**	**195 (36.9%)**	**345 (71.9%)**	**182 (37.9%)**	**335 (71.9%)**	**195 (41.8%)**
Gastrointestinal disorders						
Diarrhoea	46 (8.7%)	17 (3.2%)	46 (9.6%)	16 (3.3%)	45 (9.7%)	18 (3.9%)
Vomiting	25 (4.7%)	9 (1.7%)	17 (3.5%)	7 (1.5%)	18 (3.9%)	11 (2.4%)
General disorders and administration site conditions						
Fatigue	4 (0.8%)	3 (0.6%)	7 (1.5%)	6 (1.3%)	13 (2.8%)	10 (2.1%)
Irritability	52 (9.8%)	42 (8.0%)	56 (11.7%)	45 (9.4%)	68 (14.6%)	54 (11.6%)
Pyrexia	58 (11.0%)	42 (8.0%)	68 (14.2%)	49 (10.2%)	60 (12.9%)	47 (10.1%)
Infections and infestations						
Nasopharyngitis	38 (7.2%)	17 (3.2%)	22 (4.6%)	3 (0.6%)	18 (3.9%)	5 (1.1%)
Otitis media	28 (5.3%)	9 (1.7%)	27 (5.6%)	4 (0.8%)	18 (3.9%)	2 (0.4%)
Rhinitis	64 (12.1%)	19 (3.6%)	67 (14.0%)	21 (4.4%)	43 (9.2%)	12 (2.6%)
Upper respiratory tract infection	40 (7.6%)	6 (1.1%)	34 (7.1%)	11 (2.3%)	29 (6.2%)	17 (3.6%)
Metabolism and nutrition disorders						
Anorexia	15 (2.8%)	11 (2.1%)	2 (0.4%)	1 (0.2%)	12 (2.6%)	10 (2.1%)
Psychiatric disorders						
Crying	24 (4.5%)	13 (2.5%)	12 (2.5%)	6 (1.3%)	10 (2.1%)	8 (1.7%)
Respiratory, thoracic and mediastinal disorders						
Cough	42 (8.0%)	10 (1.9%)	36 (7.5%)	6 (1.3%)	27 (5.8%)	7 (1.5%)
Skin and subcutaneous tissue disorders						
Eczema	6 (1.1%)	2 (0.4%)	17 (3.5%)	7 (1.5%)	15 (3.2%)	9 (1.9%)
Rash	30 (5.7%)	13 (2.5%)	26 (5.4%)	9 (1.9%)	26 (5.6%)	13 (2.8%)
Rash morbilliform	21 (4.0%)	17 (3.2%)	28 (5.8%)	25 (5.2%)	32 (6.9%)	30 (6.4%)
Rash rubelliform	7 (1.3%)	6 (1.1%)	9 (1.9%)	8 (1.7%)	7 (1.5%)	6 (1.3%)
Rash vesicular	28 (5.3%)	26 (4.9%)	19 (4.0%)	18 (3.8%)	30 (6.4%)	28 (6.0%)

n (%): number (percentage) of subjects presenting at least once the considered event

[Ref. Table 12.7 of CSR MRV02C]

The percentage of subjects reporting systemic adverse events after the second dose was comparable between groups (Table 14). Among these subjects, 26.5% in Group 1, 24.5% in Group 2 and 24.2% in Group 3 experienced systemic adverse events related to ProQuad

Table 14: Systemic adverse events from Day 0 to Day 28 **post dose 2** (with an incidence >1% for vaccine-related AE)

	Group 1 Dose 1 at 9 months (N=524)		Group 2 Dose 1 at 11 months (N=474)		Group 3 Dose 1 at 12 months (N=462)	
	All	Related to ProQuad	All	Related to ProQuad	All	Related to ProQuad
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Systemic adverse event from Day 0 to Day 28	**307 (58.6%)**	**139 (26.5%)**	**272 (57.4%)**	**116 (24.5%)**	**259 (56.1%)**	**112 (24.2%)**
Gastrointestinal disorders						
Diarrhoea	22 (4.2%)	7 (1.3%)	24 (5.1%)	10 (2.1%)	20 (4.3%)	10 (2.2%)
Vomiting	15 (2.9%)	7 (1.3%)	11 (2.3%)	5 (1.1%)	8 (1.7%)	2 (0.4%)
General disorders and administration site conditions						
Fatigue	5 (1.0%)	5 (1.0%)	3 (0.6%)	3 (0.6%)	3 (0.6%)	3 (0.6%)
Irritability	39 (7.4%)	30 (5.7%)	24 (5.1%)	18 (3.8%)	29 (6.3%)	24 (5.2%)
Pyrexia	39 (7.4%)	23 (4.4%)	38 (8.0%)	23 (4.9%)	27 (5.8%)	11 (2.4%)
Infections and infestations						
Nasopharyngitis	18 (3.4%)	9 (1.7%)	25 (5.3%)	1 (0.2%)	21 (4.5%)	3 (0.6%)
Rhinitis	49 (9.4%)	16 (3.1%)	35 (7.4%)	6 (1.3%)	47 (10.2%)	16 (3.5%)
Upper respiratory tract infection	36 (6.9%)	8 (1.5%)	45 (9.5%)	13 (2.7%)	59 (12.8%)	12 (2.6%)
Psychiatric disorders						
Crying	15 (2.9%)	6 (1.1%)	7 (1.5%)	6 (1.3%)	11 (2.4%)	10 (2.2%)
Skin and subcutaneous disorders						
Eczema	15 (2.9%)	9 (1.7%)	7 (1.5%)	3 (0.6%)	7 (1.5%)	5 (1.1%)
Rash	29 (5.5%)	8 (1.5%)	16 (3.4%)	8 (1.7%)	18 (3.9%)	8 (1.7%)
Rash morbilliform	11 (2.1%)	8 (1.5%)	13 (2.7%)	10 (2.1%)	13 (2.8%)	12 (2.6%)
Rash rubelliform	8 (1.5%)	8 (1.5%)	9 (1.9%)	8 (1.7%)	4 (0.9%)	4 (0.9%)
Rash vesicular	11 (2.1%)	9 (1.7%)	18 (3.8%)	16 (3.4%)	12 (2.6%)	11 (2.4%)

n (%): number (percentage) of subjects presenting at least once the considered event

[Ref. Table 12.7 of CSR MRV02C]

Fever

After the first dose of ProQuad, the incidence of subjects with a rectal (or equivalent) temperature ≥39.4° C from Day 0 to Day 28 was significantly higher in Group 3 (14.8%) compared to Group 1 (8.8%) and Group 2 (10.3%). Differences between Groups 1 and 3 was -6.06 % [-10.17; -2.04] and between Groups 2 and 3 was -4.57 % [-8.83; -0.33]. The rate of subjects with maximal rectal (or equivalent) temperature ≥38.0° C or ≥39.4° C was the highest on the time period Day 5 to Day 12 for all study groups.

Table 15: Maximal rectal (or equivalent) temperature from Day 0 to Day 28 post dose 1

	Group 1 Dose 1 at 9 months (N=528)	Group 2 Dose 1 at 11 months (N=480)	Group 3 Dose 1 at 12 months (N=466)
	n (%)	n (%)	n (%)
Day 0 – Day 28			
≥38.0°C	245 (46.8%)	268 (56.2%)	273 (58.7%)
≥39.4°C	46 (8.8%)	49 (10.3%)	69 (14.8%)

38.0°C = 100.4°F / 39.4°C = 102.9°F

After the second dose of ProQuad, the incidence of subjects with a rectal (or equivalent) temperature ≥ 39.4° C from Day 0 to Day 28 was not significantly different between the three age 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) (Table 16). 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.

Table 16: Serious Adverse Events Occurring between the First and the Second Dose of ProQuad – Safety Set Post-Dose 1

	Group 1 Dose 1 at 9 months (N=528)	**Group 2 Dose 1 at 11 months (N=480)**	**Group 3 Dose 1 at 12 months (N=466)**
	n (%)	**n (%)**	**n (%)**
Serious adverse event	**18 (3.4%)**	**8 (1.7%)**	**8 (1.7%)**
Cardiac disorders	1 (0.2%)	0	0
Tachycardia	1 (0.2%)	0	0
Infections and infestations	14 (2.7%)	6 (1.3%)	5 (1.1%)
Bronchiolitis	1 (0.2%)	0	1 (0.2%)
Bronchitis	1 (0.2%)	2 (0.4%)	2 (0.4%)
Cellulitis	0	0	1 (0.2%)
Gastroenteritis	3 (0.6%)	3 (0.6%)	0
Gastroenteritis Norwalk virus	2 (0.4%)	0	0
Gastroenteritis rotavirus	6 (1.1%)	0	1 (0.2%)
Laryngitis	0	1 (0.2%)	0
Nasopharyngitis	1 (0.2%)	0	0
Otitis media	1 (0.2%)	0	1 (0.2%)
Otitis media acute	0	1 (0.2%)	0
Pneumonia	0	1 (0.2%)	1 (0.2%)
Pyelonephritis acute	1 (0.2%)	0	0
Sepsis	0	1 (0.2%)	0
Viral infection	1 (0.2%)	0	0
Injury, poisoning and procedural complications	1 (0.2%)	2 (0.4%)	3 (0.6%)
Concussion	0	1 (0.2%)	3 (0.6%)
Forearm fracture	0	1 (0.2%)	0
Head injury	1 (0.2%)	0	0
Nervous system disorders	2 (0.4%)	0	0
Convulsion	1 (0.2%)	0	0
Febrile convulsion	1 (0.2%)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.4%)	0	0
Asthma	1 (0.2%)	0	0
Bronchospasm	1 (0.2%)	0	0
Skin and subcutaneous tissue disorders	0	1 (0.2%)	0
Dermatitis	0	1 (0.2%)	0

n (%): number of subjects (percentage) presenting at least once the considered event

[Ref. Table 12.13 of CSR MRV02C]

Of note, the febrile convulsion reported by 1 subject in Group 1 occurred 23 days after the first dose of ProQuad and was associated with non-serious otitis media; in addition, the convulsion reported by another subject in Group 1 occurred 62 days after the first injection of ProQuad, in a context of clinically diagnosed varicella but without fever at the time of the convulsion, the subject however had febrile convulsion in her medical history, the event was assessed as a non-serious event by the investigator, but it was upgraded by the company as a serious adverse event.

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.

2.3.3. Discussion

The CHMP noted that the percentage of vaccine related systemic adverse reactions including fever reactions is comparable between all three age groups following the first and second vaccination with ProQuad. Vaccination of infants from 9-11 months of age does not result in an increase in adverse reactions compared with children aged 12 months at the time of first vaccination.

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). However, 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. In summary, 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.The CHMP highlighted that the current safety profile, especially the higher risk of febrile convulsions following the first dose of ProQuad compared to MMR and varicella vaccines, suggests to use ProQuad in subject aged 9 months only under special circumstances.

Overall, the safety data observed in this clinical trial for the two dose regimen are adequate to support the conclusion that ProQuad was as well tolerated in the 9 months old vaccinees as in the 11 and 12 months old vaccinees. The younger age group of children with 9 months at the time of Dose 1 tolerated the two vaccinations of ProQuad with a comparable safety profile of the children aged 11 and 12 months at the time of Dose 1.

2.4. Risk management plan

No revision of the current version 4.0 of the Risk management Plan for ProQuad is required. The complete safety data set of study MRV02C is already considered in the current RMP. In addition no new safety concern was identified in children 9 to 12 months of age compared to children from 12 months of age onwards.

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.5. Changes to the Product Information

During the procedure, the CHMP requested the following additional amendments to the Product Information:

Section 4.1 of the SmPC:

The initial proposal from the MAH to include day-care as one of the special circumstances under which ProQuad can be administered from 9 months of age onwards was not considered acceptable, as this term is likely to be interpreted differently across Europe. In addition, the risk of measles infection in day-care is not well supported by epidemiological data, e.g. in case of no outbreak.

The complete indication approved is as follows:

ProQuad is indicated for simultaneous vaccination against measles, mumps, rubella and varicella in individuals from 12 months of age.

ProQuad can be administered to individuals from 9 months of age under special circumstances (e.g., to conform with national vaccination schedules, outbreak situations, or travel to a region with high prevalence of measles; see sections 4.2, 4.4, and 5.1).

Section 4.2 of the SmPC:

This section was revised to highlight that the use of ProQuad should be based on official recommendations, to better clarify the dosage recommendations for individuals 12 months of age or older and individuals between 9 and 12 months of age, and to highlight that the safety and efficacy of ProQuad in children under 9 months of age has not been established.

Package Leaflet:

As the use of the term “you or your child” could be misleading it is proposed to replace it with “the person to be vaccinated”:

Information provided in the package leaflet was aligned to the revised SmPC

Changes were also made to the PI to bring it in line with the current QRD template, SmPC guideline and other relevant guidelines, which were reviewed by QRD and accepted by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

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 only under special circumstances as outlined above. While the immune responses against mumps, rubella and varicella were comparable between the groups, the data clearly indicate that vaccination of infants at 9 months of age results in lower antibody responses as regards measles. The lower antibody responses are most likely due to interfering pre-existing maternal antibodies or to the immaturity of the immune response of these children.

Therefore additional vaccine doses are warranted later on in life and in order to provide adequate protection a second dose has to be administered given a minimum of 3 months apart.

No information on the effect of an additional dose of a measles containing vaccine to the primary immunisation course of ProQuad is currently available and in any case the current public health effort to eliminate measles and congenital rubella shortly would require the use of the most efficient schedule providing protection with the lowest number of administrations.

As regards to safety the incidence and intensity of adverse reactions was comparable in infants 9 months of age with infants 12 months of age.

The benefit risk balance is favourable for subjects aged 9 to 12 months receiving ProQuad only under special circumstances, when the risk of acquiring measles is particularly high.

The MAH provided with the submission a revised product information to include immunogenicity and safety results of study MRV02C. During the procedure, further amendments were made for sections 4.1 and 4.2 in line with the CHMP recommendations.

Taking into account the available efficacy and safety data and the resulting update of the Product Information, the CHMP considered that the benefit-risk balance for ProQuad remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include use from 9 months of age onwards under special circumstances.

Furthermore, the PI is being brought in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

The PSUR cycle for the medicinal product should follow a 6 monthly cycle, unless otherwise agreed by the CHMP.