30 May 2013
EMA/71891/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Proquad

International non-proprietary name: measles, mumps, rubella and varicella vaccine (live)

Procedure No.: EMEA/H/C/000622/X/0068

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Background information on the procedure

1.1. Requested Extension

The MAH submitted on 20 December 2012 to the European Medicines Agency (EMA) an application for an extension of the Marketing Authorisation (MA) pursuant to Article 19 of Commission Regulation (EC) No 1234/2008.

The MAH applied for the addition of a new route of administration, Intramuscular use, leading to an amendment of the existing marketing authorisation.

The clinical data supporting the addition of the intramuscular administration (study F05-MMRV-304) were previously submitted in the context of FUM 025, which was assessed and concluded in August 2010. The MAH proposed with the current application to update sections 4.2, 4.4, 4.8 and 5.1 of the SmPC. The Package Leaflet and Labelling were proposed to be updated in accordance.

No data regarding quality have been included in the submission as the product itself would not change neither have new presentations.

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

Information on Paediatric requirements

Not applicable

Licensing status

Proquad has been authorised in the European Union (EU) on 6 April 2006.

1.2. Steps taken for the assessment of the product

The Rapporteurs appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus

Co-rapporteur: Daniela Melchiorri

- The application was received by the EMA on 20 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's final Assessment Report was circulated to all CHMP members on 17 May 2013.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension to the existing Marketing Authorisation of Proquad.

2. Scientific discussion

2.1. Introduction

ProQuad has been licensed in Europe since April 2006. 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.

The licensed route of administration for ProQuad is the subcutaneous (SC) route. In many Member States healthcare providers administer measles, mumps, rubella and varicella (MMRV) vaccines by the intramuscular (IM) route. A recent study has demonstrated that both IM and SC routes of administration of the MAH's combined MMR (M-M-RVAXPRO) or varicella vaccine (Varivax), containing the same virus components, elicit similar immunogenic responses and display similar safety and tolerability profiles.

The primary aim of study F05-MMRV-304 (EudraCT: 2006-001986-40) was to demonstrate that two doses of ProQuad administered by the IM route are as immunogenic as two doses of ProQuad administered by the SC route to healthy children 12 to 18 months of age. Additionally, the study was designed to investigate the antibody titres and immune response rates to measles, mumps, rubella and varicella four weeks after the first dose and the antibody titres six weeks after the second dose of ProQuad administered by the IM or the SC route and to investigate the safety profile after each of the two doses of ProQuad both administered either by the IM or the SC route to healthy children 12 to 18 months of age. ProQuad was expected to provide similar immunogenicity against measles, mumps, rubella, and varicella by the IM route as the concomitant administration of M-M-R II and VARIVAX as previously demonstrated. For regulatory acceptance the MAH committed to confirm in an immunogenicity and safety trial that IM and SC administration of ProQuad are comparable (ref also to FUM 025).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH.

Table 1 Tabular overview of the clinical study

Types of Study	Study Identifier	Location for Study Report	Objective of the Study	Study Design and Type of Control	Study Vaccines: Dosing Schedule; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis Patients	Duration of Vaccination Period	Study Status; Type of Report
Immunoge-nicity and safety	F05-MMRV-304	Module 5	**Primary objective:** To demonstrate that 2 doses of ProQuad administered by the IM	Open-label, randomised, multicentre study with two parallel groups	Subjects were randomised in a 1:1 ratio to receive at Visit 1 (Day 0): Group 1: Dose 1 of ProQuad by	380 subjects (190 per group)	Healthy infants aged 12 to 18 months without vaccination history and /or	Between 30 to 44 days follow-up after Dose 1 and between 42 to 56 days follow up after	Complete; Full

			route are as immunogenic as 2 doses of ProQuad administered by the SC route to healthy children 12-18 months of age. **Secondary objectives:** To describe the antibody response rates to measles, mumps, rubella and after Dose 1 of ProQuad and titres to measles, mumps, rubella and varicella after Dose 2 of ProQuad administered by the IM or SC route. To describe the safety profile of each of the 2 doses of ProQuad, both administered either by the IM or SC route.		the IM route at 12 to 18 months of age, and Dose 2 by the IM route 30 days later. Group 2: Dose 1 of ProQuad by the SC route at 12 to 18 months of age, and Dose 2 by the SC route 30 days later.		suspected clinical history and/or exposure in the past 30 days to measles, mumps, rubella, varicella and/pr zoster.	Dose 2, i.e. between 72 and 100 days follow-up after Dose 1 in each group.	

2.4. Design and conduct of the clinical study

Study F05-MMRV-304 was a Phase IIIb, open-label, randomised, two groups, comparative, multicentre study carried out in France.

Study subjects and treatments

During the study 380 healthy seronegative children of either gender aged between 12 and 18 months were planned to be enrolled in 40 centres in France and to be randomly assigned to one of the two study groups to receive ProQuad either by the IM or SC route. The administration schedule of ProQuad was as recommended (i.e. two doses administered at least 1 month apart) in the Summary of Product Characteristics (SmPC).

The use of an anaesthetic cream or patch at the injection site was not allowed. The site of administration was the upper arm.. The second dose was administered in the contra-lateral arm.

Three visits were foreseen: Inclusion Visit (Day 0 = first dose), Visit 2 (second dose) between Day 30 and Day 44 after Visit 1, and Visit 3 between Day 42 and Day 56 after Visit 2.

Three blood samples were collected from subjects participating in the study:

- The first blood sample (BS1) was collected after the subject's eligibility had been verified and the informed consent signed by both holders of the parental authority or by the legal representative. This had to be within seven days before or at the time of Visit 1, and before the first vaccination.

- The second blood sample (BS2) was collected between Day 30 and Day 44 post dose 1 and prior to dose 2.

- The third blood sample (BS3) was collected between Day 42 and Day 56 post dose 2.

Objectives

Primary objective

To demonstrate that two doses of ProQuad administered by the IM route are as immunogenic as two doses of ProQuad administered by the SC route to healthy children 12 to 18 months of age in terms of antibody response rates to measles, mumps and rubella measured by ELISA and to varicella measured by gpELISA at 42 days following the second dose of ProQuad.

For each of the four antigens tested (i.e. measles, mumps, rubella and varicella), the primary hypothesis was that the IM route would be non-inferior to the SC route.

Secondary objectives

- To describe the antibody response rates to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad administered by the IM or SC route.

- To describe the antibody titres to measles, mumps, rubella and varicella 30 days after the first dose of ProQuad and 42 days after the second dose of ProQuad, both administered by the IM or SC route.

- To describe the safety profile of each of the two doses of ProQuad, both administered either by the IM or SC route.

Criteria for evaluation

- Immunogenicity:

Primary criterion: Antibody response rates to measles, mumps, rubella and varicella measured six weeks after the second dose of ProQuad in both groups (BS3).

Secondary criteria:

- Antibody response rates to measles, mumps, rubella and varicella measured four weeks after the first dose of ProQuad in both groups (BS2).
- Antibody titres to measles, mumps, rubella and varicella measured four weeks after the first dose of ProQuad (BS2) and six weeks after the second dose of ProQuad (BS3) in both groups.
- Rates of subjects with varicella antibody titres ≥1.25 gpELISA units/mL in subjects whose baseline varicella antibody titre (BS1) was <1.25 gpELISA units/mL, four weeks after the first dose of ProQuad (BS2) and six weeks after the second dose of ProQuad (BS3) in both groups.

- Safety:

From Day 0 to Day 4 following each dose: Solicited injection-site adverse reactions including injection-site erythema, swelling and pain.

From Day 0 to Day 28 following each dose: unsolicited injection-site adverse reactions and systemic adverse events:

- Unsolicited injection-site adverse reactions, including injection-site erythema, injection-site swelling and injection-site pain starting from Day 5 to Day 28.
- Rectal temperature (≥38.0°C or, if missing, axillary temperature ≥37.1°C and ≥39.4°C or, if missing, axillary temperature ≥38.5°C).
- Measles-like, rubella-like, varicella-like and zoster-like rash, mumps-like illness.
- Other systemic adverse events.

From Day 0 to the last visit of the concerned subject: serious adverse events.

Determination of Sample Size

Table 2 Power of the study per valence and overall for the Per Protocol Analysis assuming 190 subjects included per group

Valence	Rate of seropositivity at inclusion	Rate of non-compliance and drop-out up to Dose 2	Number of evaluable subjects	Expected response rates	α	Δ	Power
Measles, mumps, or rubella	5%	15%	152	97%	2.5%	10%	98.9%
Varicella	10%	15%	142	95%	2.5%	10%	93.0%
Overall Power							90.1%

The overall power of the study should be around 90% for the success of the primary objective. The enrolled sample size would therefore be 190 subjects in each group for a total sample size of 380 subjects.

The study design was found appropriate with satisfying inclusion and exclusion criteria and randomisation procedure.

Statistical Methods

Immunogenicity

Primary criteria: The main analysis evaluated the immunogenicity after the second dose of ProQuad based on the Per Protocol Sets Post-dose 2 stratified by region (i.e., pooled centres based on geographic location); the statistical analysis was based on two-sided 95% (adjusted for multiplicity) confidence interval (CI) around the difference in response rates [Group 1 (IM) – Group 2 (SC)] for each valence. The non-inferiority criterion was achieved if the lower bound of the 95% CI was >(-10) percentage points.

The supportive analysis evaluated the immunogenicity based on the Per Protocol Sets Post-dose 2 not stratified by region and on the Full Analysis Set (stratified by region and not stratified).

Secondary criteria: A descriptive analysis within each group was performed for measles, mumps, rubella and varicella including the calculation after each dose of the GMTs (and 95% CIs), the response rates (and 95% CIs) and the rates (and 95% CIs) of subjects with varicella antibody titres ≥1.25

gpELISA units/mL in subjects whose baseline varicella antibody titre was <1.25 gpELISA units/mL (seronegative antibody titre).

Safety:

The safety analysis of each dose of ProQuad was descriptive.

Data sets analysed

The Randomised Set was defined as all randomised subjects.

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.

Two Per Protocol Sets were defined with one for the analysis of the immunogenicity criteria Post-dose 1 (Per Protocol Set Post-dose 1 [PPS1]) and a second for the analysis of the immunogenicity criteria Post-dose 2 (Per Protocol Set Post-dose 2 [PPS2]).

2.5. Immunogenicity results

During the recruitment period 411 healthy children aged 12 to 18 months were selected and thereof 405 children were randomly allocated to one of the two vaccination groups (Table 1). All subjects attended Visit 1 and Visit 2, whereas one subject in the IM group and three in the SC group did not attend Visit 3. All subjects received both doses of the study vaccine.

Table 3: Disposition of subjects

	Group 1 INTRAMUSCULAR	Group 2 SUBCUTANEOUS	All
N selected			411
N randomised	202	203	405
N vaccinated – First dose	202 (100%)	203 (100%)	405 (100%)
N vaccinated – Second dose	202 (100%)	203 (100%)	405 (100%)
N completed	201 (99.5%)	200 (98.5%)	401 (99.0%)
N withdrawn	1 (0.5%)	3 (1.5%)	4 (1.0%)
Reason for withdrawal			
Lost to follow-up	1 (0.5%) (1)	2 (1.0%) (2)	3 (0.7%)
Non-compliance with protocol	0	1 (0.5%) (3)	1 (0.2%)

Percentages are calculated based on the number of randomised subjects
(1) Subject 42004
(2) Subjects 35007 and 44002
(3) Subject 38008

The **PPS1** of subjects initially seronegative to measles (titre <255 mIU/mL) consisted of 153 (75.7%) subjects in the IM group and 148 (72.9%) in the SC group, the PPS1 of subjects initially seronegative to mumps (titre <10 ELISA Ab units/mL) consisted of 152 (75.2%) subjects in the IM group and 149 (73.4%) in the SC group; the PPS1 of subjects initially seronegative to rubella (titre <10 IU/mL) consisted of 129 (63.9%) subjects in the IM group and 133 (65.5%) in the SC group; the PPS1 of subjects initially seronegative to varicella (titre <1.25 gpELISA units/mL) consisted of 138 (68.3%) subjects in the IM group and 136 (67.0%) in the SC group.

The **PPS2** of subjects initially seronegative to measles (titre <255 mIU/mL) consisted of 153 (75.7%) subjects in the IM group and 147 (72.4%) in the SC group; the PPS2 of subjects initially seronegative to mumps (titre <10 ELISA Ab units/mL) consisted of 152 (75.2%) subjects in the IM group and 148 (72.9%) in the SC group; the PPS2 of subjects initially seronegative to rubella (titre <10 IU/mL)

consisted of 129 (63.9%) subjects in the IM group and 132 (65.0%) in the SC group; the PPS2 of subjects initially seronegative to varicella (titre <1.25 gpELISA units/mL) consisted of 138 (68.3%) subjects in the IM group and 134 (66.0%) in the SC group.

Demographic and other Baseline Characteristics

As shown in Table 2 for the Randomised Set the mean age at first vaccination was 13.68 (±1.48) months and the gender distribution was 50.9% male and 49.1% female.

The FAS, PPS1, PPS2, Safety Set Post-dose 1 and Safety Set Post-dose 1 were comparable to the Randomised Set. The two groups were comparable with respect to the mean time between first vaccination to BS2 (36.1 ±6.3 days) and second vaccination to BS3 (46.2 ±5.5 days).

Table 4: Demographic and other Baseline Characteristics – Randomised Set

	Group 1 INTRAMUSCULAR N=202	Group 2 SUBCUTANEOUS N=203	All N=405
Age (Months) at 1st Vaccination			
n	202	203	405
Mean (SD)	13.72 (1.44)	13.65 (1.53)	13.68 (1.48)
Median	13.30	13.30	13.30
Minimum - Maximum	11.9 ; 18.0	11.7 ; 18.3	11.7 ; 18.3
Gender			
n	202	203	405
Male n (%)	97 (48.0%)	109 (53.7%)	206 (50.9%)
Female n (%)	105 (52.0%)	94 (46.3%)	199 (49.1%)
Weight (kg)			
n	202	203	405
Mean (SD)	10.0 (1.1)	9.9 (1.1)	9.9 (1.1)
Median	10.0	10.0	10.0
Minimum - Maximum	7 ; 13	7 ; 13	7 ; 13
Height (cm)			
n	202	203	405
Mean (SD)	77.3 (3.2)	77.0 (3.3)	77.2 (3.3)
Median	77.5	77.0	77.0
Minimum - Maximum	70 ; 89	66 ; 87	66 ; 89

Between Visit 1 and Visit 3, 359 subjects (88.6%) reported the intake of at least one concomitant medication, a rate that was comparable between the two groups. The most frequently reported concomitant medication was in the category nervous system (75.7% in the IM group and 73.9% in the SC group), i.e. mainly analgesics, followed by respiratory system (61.9% in the IM group and 60.6% in the SC group), i.e. mainly nasal preparations and cough and cold preparations, and anti-infectives for systemic use (39.6% in the IM group and 39.9% in the SC group), i.e. mainly antibacterial for systemic use.

Results

Primary objective

For both IM and SC groups, the antibody response rates to measles, mumps, rubella and varicella were >99% at six weeks after the second dose of ProQuad for the subjects initially seronegative to measles, mumps, rubella or varicella (see Table 5).

Table 5: Summary and Non-inferiority Analysis (Stratified by Region) of Antibody Response Rates to Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad for Subjects Initially Seronegative to Measles, Mumps, Rubella or Varicella – Antigen Specific PPS 2

	Group 1 INTRAMUSCULAR		Group 2 SUBCUTANEOUS		Difference [Group 1 (IM) – Group 2 (SC)]	[95% CI]	Non-inferiority
	N	Number of responders (Response rate) [95% CI]	N	Number of responders (Response rate) [95% CI]			
Measles	153	153 (100) [97.6 ; 100]	147	147 (100) [97.5 ; 100]	0.0%	[-2.5 ; 2.6]	Yes
Mumps	152	151 (99.3) [96.4 ; 100]	148	147 (99.3) [96.3 ; 100]	0.1%	[-3.0 ; 3.3]	Yes
Rubella	129	129 (100) [97.2 ; 100]	132	131 (99.2) [95.9 ; 100]	0.7%	[-2.3 ; 4.1]	Yes
Varicella	138	138 (100) [97.4 ; 100]	134	133 (99.3) [95.9 ; 100]	0.7%	[-2.1 ; 4.1]	Yes

Response rates 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.

The lower bound of the two-sided 95% CI on the difference in antibody response rates for all antigens was greater than -10%. Therefore, in all cases the difference was statistically significantly lower than the pre-defined clinically relevant non-inferiority margin of -10%. Non-inferiority of the response rates to all antigens following 2 doses of ProQuad administered IM vs. SC was therefore established.

Consequently, the primary objective of this study has been met since a 2-dose regimen of ProQuad administered by the IM route is as immunogenic as a 2-dose regimen of ProQuad administered by the SC route, regarding response rates to measles, mumps, rubella and varicella at six weeks post-vaccination.

Although the PPS and the FAS were different in terms of number of patients analysed, response rates to measles, mumps, rubella and varicella, as well as non-inferiority results obtained with and without stratification by geographic region, were also similar in both groups in the FAS.

Secondary objectives

- Antibody Response Rates after the First Dose of ProQuad

Four weeks after the first dose of ProQuad, response rates for measles, rubella and varicella were numerically similar in both groups. The response rate for mumps was numerically higher in the IM group. The mumps and varicella antibody response rates were higher post-Dose 2 of ProQuad in both groups. Results were similar in the FAS.

Table 6: Summary of Antibody Response Rates to Measles, Mumps, Rubella and Varicella 4 Weeks after the First Dose of ProQuad for Subjects Initially Seronegative to Measles, Mumps, Rubella or varicella – Antigen Specific PPS 1

	Group 1 INTRAMUSCULAR			Group 2 SUBCUTANEOUS		
	N	Number of responders (Response rate)	[95% CI]	N	Number of responders (Response rate)	[95% CI]
Measles	153	153 (100)	[97.6 ; 100]	148	144 (97.3)	[93.2 ; 99.3]
Mumps	152	148 (97.4)	[93.4 ; 99.3]	149	136 (91.3)	[85.5 ; 95.3]
Rubella	129	127 (98.4)	[94.5 ; 99.8]	133	133 (100)	[97.3 ; 100]
Varicella	138	136 (98.6)	[94.9 ; 99.8]	136	134 (98.5)	[94.8 ; 99.8]

Response rates 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.

- Antibody Titres (GMT) after the First and Second Doses of ProQuad

Measles, mumps, rubella and varicella GMTs were comparable in the two groups after the first and the second doses of ProQuad.

Table 7: Summary of Geometric Mean Titres to Measles, Mumps, Rubella and Varicella 4 Weeks after the First Dose of ProQuad for Subjects Initially Seronegative to Measles, Mumps, Rubella or Varicella – Antigen Specific PPS 1

	Group 1 INTRAMUSCULAR			Group 2 SUBCUTANEOUS		
	N	GMT Post-dose 1	[95% CI]	N	GMT Post-dose 1	[95% CI]
Measles (mIU/mL)	153	4058.7	[3643.1 ; 4521.8]	148	3327.0	[2835.4 ; 3903.9]
Mumps (ELISA Ab units/mL)	152	120.0	[102.2 ; 140.9]	149	101.9	[84.2 ; 123.2]
Rubella (IU/mL)	129	46.9	[39.7 ; 55.4]	133	50.9	[44.9 ; 57.7]
Varicella (gpELISA units/mL)	138	25.0	[22.5 ; 27.7]	136	23.6	[20.9 ; 26.7]

Measles GMTs were also comparable after the first and the second doses. Mumps, rubella and varicella GMTs were numerically higher after the second dose of ProQuad than after the first dose, the most robust boosting effect being observed for varicella. Results were similar in the FAS.

Table 8: Summary of Geometric Mean Titres to Measles, Mumps, Rubella and Varicella 6 Weeks after the Second Dose of ProQuad for Subjects Initially Seronegative to Measles, Mumps, Rubella or Varicella – Antigen Specific PPS 2

	Group 1 INTRAMUSCULAR			Group 2 SUBCUTANEOUS		
	N	GMT Post-dose 2	[95% CI]	N	GMT Post-dose 2	[95% CI]
Measles (mIU/mL)	153	3953.7	[3497.2 ; 4469.9]	147	3748.6	[3270.9 ; 4296.0]
Mumps (ELISA Ab units/mL)	152	157.9	[138.6 ; 180.0]	148	168.8	[146.9 ; 194.0]
Rubella (IU/mL)	129	92.8	[82.4 ; 104.5]	132	94.2	[83.2 ; 106.6]
Varicella (gpELISA units/mL)	138	358.1	[300.1 ; 427.4]	134	261.8	[216.7 ; 316.4]

- Rate of Subjects with Varicella Antibody Titre ≥1.25 gpELISA units/mL after the First and Second Doses of ProQuad

Following both the first and second doses of ProQuad, the rates of subjects with varicella antibody titre ≥1.25 gpELISA units/mL were similar in both groups.

Table 9: Rates of Subjects with Varicella antibody titre ≥1.25 gpELISA units / mL 4 Weeks after the First Dose and 6 Weeks after the Second Dose of ProQuad – Per Protocol Sets Post-dose 1 and Post-dose 2 for Varicella

Varicella antibody titre >=1.25 gpELISA units /mL	Group 1 - INTRAMUSCULAR			Group 2 - SUBCUTANEOUS		
	N	n subjects (%)	[95% CI]	N	n subjects (%)	[95% CI]
Post-dose 1	138	138 (100)	[97.4; 100]	136	135 (99.3)	[96.0; 100]
Post-dose 2	138	138 (100)	[97.4; 100]	134	133 (99.3)	[95.9; 100]

2.5.1. Conclusions on immunogenicity

The results presented demonstrate no difference between the IM and the SC routes of administration in terms of immunogenicity parameters following a 2 dose regimen. The post-dose 2 response rates and GMTs were generally comparable for all vaccine components. Regarding mumps higher response rates were obtained post dose 1 following intramuscular administration (IM: 97.4% vs SC: 91.3%).

2.6. Clinical safety

The Safety Set considered all subjects who received at least one dose of the study vaccine and had safety follow-up data up to 30 to 44 days post dose 1 and up to 42 to 56 days post dose.

Patient exposure

All subjects received both vaccinations and had safety follow-up data after receiving the first dose of ProQuad (202 in the IM group and 203 in the SC group). 201 subjects in the IM group and 200 subjects in the SC group had safety follow-up data after receiving the second dose of ProQuad. Consequently, there were two sub-sets for the safety analysis: Safety Set Post-dose 1 – after the first vaccination with ProQuad and Safety Set Post-dose 2 - after the second vaccination with ProQuad.

Adverse events

Following the **first dose** of ProQuad, injection-site adverse reactions from Day 0 to Day 28 were reported by fewer subjects in the IM group (17.8%) than in the SC group (28.6%). Most reactions started during the first four days after vaccination. The incidences were higher in the SC group than in the IM group for injection-site erythema (14.3% in the SC group vs. 5.0% in the IM group) and injection-site swelling (3.9% in the SC group vs 1.0% in the IM group). Conversely, injection-site pain was more frequent in the IM group than in the SC group (10.9% in the IM group vs. 5.9% in the SC group). No injection-site adverse reaction was described as being of severe intensity. There was no injection-site rash of interest in the IM group, whereas there were two reports in the SC group (1 rubella-like rash and 1 varicella-like rash).

Concerning systemic adverse events, the incidences were similar in the two groups (78.2% in the IM group and 82.3% in the SC group).

In addition, the incidence of non-injection-site rashes of interest was similar in both groups (4.5% in the IM group and 5.4% in the SC group). There were more cases of measles/measles-like rash in the SC group than in the IM group: four and one, respectively. Conversely, there were two cases of varicella/varicella-like rash in the IM group and one in the SC group. One mumps/mumps-like illness was reported in the IM group ('parotid gland enlargement', severe intensity), and none in the SC group.

Regarding body temperature ≥39.4°C (rectal equivalent) measured between Day 5 and Day 12, the incidence was 13.1% in the IM group and 11.1% in the SC group.

A 13-month-old male subject without medical history of seizure, experienced moderate febrile seizure, 31 days after receiving the first dose of ProQuad by the subcutaneous route. It was considered not to be vaccine related.

Table 10: Adverse events after first dose

First dose	Group 1, i.m. N=202		Group 2, s.c. N=203	
	n	%	n	%
Injection-site or systemic adverse event from Day 0- Day 28	163	80.7	175	86.2
Solicited injection-site adverse reactions from Day 0 to Day 4	31	15.3	44	21.7
Erythema	10	5.0	29	14.3
Swelling	2	1.0	8	3.9
Pain	22	10.9	12	5.9
Pyrexia (Day 5-12)				
<39.4°C or normal	172	86.9	176	88.9
≥39.4°C	26	13.1	22	11.1
Other systemic event from Day 0 to Day 28				

- All - Vaccine related	122 18	60.4 8.9	121 17	59.6 8.4

Following the **second dose** of ProQuad (Day 0 to Day 28), similarly to what has been observed after the first dose, there were fewer reports of injection-site adverse reactions in the IM group (20.4%) than in the SC group (29.5%). Most injection-site adverse reactions occurred during the first four days after injection and the imbalance in favour of the IM group was due to injection-site erythema (15.4% in the IM group vs. 27.0% in the SC group) and injection-site swelling (6.0% in the IM group vs. 12.5% in the SC group). The incidence of injection-site pain was the same in both groups (10.0%). Only one subject reported an injection-site adverse reaction of severe intensity (pain, in the IM group).

There was only one report of an injection-site rash of interest (measles in the SC group) and one report of a mumps/mumps-like illness, 'parotid gland enlargement', (IM group, moderate intensity, this subject reported the same event following the first dose).

Concerning systemic adverse events, the incidences were comparable in the two groups (67.7% in the IM group and 61.0% in the SC group).

There were twice as many reports of non-injection-site rashes of interest in the SC group (4.0%) compared with the IM group (2.0%). No measles/measles-like rash or varicella/varicella-like rash was reported in the IM group compared to six subjects in the SC group.

Regarding body temperature ≥39.4°C (rectal equivalent) measured between Day 5 and Day 12, the incidence was 4.1% in the IM group and 7.3% in the SC group.

Table 11: Adverse events after second dose

Second dose	Group 1, i.m. N=201		Group 2, s.c. N=200	
	n	%	n	%
Injection-site or systemic adverse event from Day 0- Day 28	150	74.6	144	72.0
Solicited injection-site adverse reactions from Day 0 to Day 4	41	20.4	59	29.5
Erythem	31	15.4	54	27.0
Swelling	12	6.0	25	12.5
Pain	20	10.0	20	10.0
Pyrexia (Day 5-12)				
<39.4°C or normal	187	95.9	177	92.7
≥39.4°C	8	4.1	14	7.3
Other systemic event from Day 0 to Day 28				
- All	114	56.7	98	49.0
- Vaccine related	12	6.0	10	5.0

The second dose of ProQuad was generally better tolerated than the first in both groups. In the IM group, 52.0% of subjects reported an injection-site adverse reaction or vaccine-related systemic adverse event after the first dose of ProQuad compared to 34.8% after the second dose of ProQuad, and 56.2% and 42.5%, respectively, in the SC group. The difference was mainly due to the systemic adverse event pyrexia. After the first dose, in the IM group 56.9% of subjects reported pyrexia (≥38.0°C rectal) compared to 44.3% after the second dose, and 61.6% and 41.0%, respectively, in the SC group (Day 0 to Day 28). Regarding vaccine-related pyrexia, the difference was more striking, with twice as many subjects reporting vaccine-related pyrexia after the first dose of ProQuad compared to the second dose in both the IM group and the SC group.

In addition, fewer subjects had a body temperature (rectal equivalent) ≥39.4°C between Day 5 and Day 12 after the second dose of ProQuad than after the first dose (IM group: 13.1% after the first dose vs. 4.1% after the second dose and SC group: 11.1% after the first dose vs. 7.3% after the second dose).

Further evaluation of adverse events assessed as 'of interest' such as seizures, myalgia, arthralgia, malaise, dizziness or fatigue, or terms with similar medical meaning, shows that 3 subjects reported such events during this study:

- one case of non-serious asthenia of moderate intensity occurred 7 days after the first dose of ProQuad administered subcutaneously, which resolved spontaneously within 70 days, and was considered by the investigator to be possibly related to vaccination. Asthenia was associated with fever, starting also 7 days after vaccination and lasting for 4 days, with a maximum of 39.1°C.
- one subject reported non-serious weakness of mild intensity, 8 days after the second dose of ProQuad administered intra-muscularly, which resolved spontaneously within 3 days, and was considered by the investigator to be possibly related to vaccination. Weakness was associated with fever of 38.6°C starting 2 days after weakness, and lasting for less than 24 hours.
- one subject reported non-serious hip inflammation of mild intensity, 19 days after the second dose of ProQuad administered intra-muscularly, considered by investigator to be not-related to vaccination. Hip inflammation was associated with fever starting 3 days after hip inflammation, with a maximum of 39.2°C and lasting for 9 days.

The majority of systemic adverse events reported from Day 0 to Day 28 were considered unrelated to vaccination by the investigator and were bronchiolitis (4% in the IM group and 1.5% in the SC group, all unrelated to vaccination); tracheitis (7.5% in the IM group and 3.0% in the SC group, all unrelated to vaccination); and cough (5.5% in the IM group and 3.5% in the SC group, 2 events in each group considered as vaccine-related).

Serious adverse event / deaths / other significant events

There were six serious adverse events reported after vaccination during the study. In each group (IM and SC), there were two serious adverse events reported after the first vaccination with ProQuad and one after the second vaccination. None of these events was considered by the investigator to be vaccine-related. No anaphylactic event or vaccine-related febrile seizure was reported during the study.

In addition, one subject reported a serious adverse event between signature of the Informed Consent Form and the first vaccination. This subject was not randomised in the study.

No subject died during the course of the study.

Laboratory findings

Not applicable.

Discontinuation due to adverse events

No subject was withdrawn from the study due to an adverse event.

2.6.1. Discussion on clinical safety

Administration of ProQuad by the intramuscular route demonstrated an acceptable safety profile post dose 1 and 2. The safety profile was comparable for both administration groups except for local reactions. Injection-site adverse reactions (injection-site erythema and injection site swelling) were experienced in fewer subjects in the IM group after each dose. While up to 4 days post dose 1 pain was reported more frequently in the IM group, the incidence of injection-site pain was the same in both administration groups post dose 2.

The second dose of ProQuad was generally better tolerated than the first dose in both groups. No safety concern was identified.

2.6.2. Conclusions on clinical safety

The safety profile after the first and second administration of ProQuad indicates that both routes of administration are comparable.

2.7. Risk management plan

The current Risk Management Plan (RMP) version 4.0 for ProQuad covers the addition of the intramuscular (IM) use as new route of administration submitted in the scope of this extension as referred to in Annex I of Regulation (EC) N°1234/2008.

The current RMP for ProQuad was developed based on safety data from the completed clinical trial F05-MMRV-304 (MAH-sponsored) which was conducted in children 12 to 18 months to compare the immunogenicity and safety of ProQuad by either IM or SC injection.

2.8. Update of the product information

As a consequence of this new route of administration, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Also Annex II has been amended according to the current QRD template.

The amendments to the respective sections of the SmPC are as follows:

Section 4.2

Method of administration

~~The vaccine is to be injected by the subcutaneous route in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.~~

The vaccine is to be injected intramuscularly (IM) or subcutaneously (SC).

The preferred injection sites are the anterolateral area of the thigh in younger children and the deltoid area in older children, adolescents, and adults.

The vaccine should be administered subcutaneously in patients with thrombocytopenia or any coagulation disorder.

Section 4.4

Thrombocytopenia

This vaccine should be given subcutaneously to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

Section 4.8

Children who received ProQuad intramuscularly

The general safety profiles of the IM and SC administration routes were comparable; however, fewer subjects experienced injection-site adverse reactions in the IM group after each dose (see section 5.1 for study description).

Section 5.1

Children who received 2 doses of ProQuad intramuscularly or subcutaneously

In a clinical trial, 405 children received 2 doses of ProQuad, either by the IM or SC route of administration. Two doses of ProQuad administered by the IM route of administration were as immunogenic as two doses administered by the SC route in terms of antibody response rates and antibody titres to measles, mumps, rubella, and varicella.

The Package Leaflet was updated accordingly.

However, to be in line with the SmPC guideline the MAH was requested to amend sections 2 and 3 of the Package leaflet to include a statement on the administration of the vaccine in subjects with thrombocytopenia or any coagulation disorders. The following statements were included:

Section 2

If you have a blood clotting disorder or low levels of platelets in your blood, the injection will be given under the skin.

Section 3

If the person to be vaccinated has a blood clotting disorder or low levels of platelets, the vaccine should be given under the skin because bleeding may occur following administration into the muscle.

Additionally minor typographic amendments were made, and the MAH took advantage of the opportunity to update the list of local representatives to include Croatia.

3. Benefit-risk balance

Benefits

Beneficial effects

Healthcare providers routinely administer live attenuated measles, mumps, rubella and varicella vaccines by the intramuscular route. Administration of ProQuad by the intramuscular route elicits comparable response rates to all vaccine components as compared to SC administration. Regarding mumps higher response rates were observed post dose 1 following intramuscular administration.

IM administration results in fewer subjects experiencing injection-site erythema and swelling.

Uncertainty in the knowledge about the beneficial effects

No clinical study data on IM administration of ProQuad are available in adolescents and adults.

Risks

Unfavourable effects

No specific unfavourable effects pertaining to the IM administration were identified.

Uncertainty in the knowledge about the unfavourable effects

No clinical study data on IM administration of ProQuad are available in adolescents and adults.

Benefit-risk balance

Importance of favourable and unfavourable effects

Since IM administration is current practice by many HCP the approval of the IM route will reduce off-label use. Based on the data assessed, it is not to be expected that IM administration of ProQuad to adolescents and adults will result in a different immunogenicity and safety profile compared to SC administration.

Discussion on the benefit-risk balance

The benefit-risk balance remains positive.

4. Recommendations

Based on the CHMP review of data on safety and efficacy, the CHMP recommends by consensus the granting of an extension of the Marketing Authorisation for the addition of a new route of administration, Intramuscular use, for the above mentioned medicinal product.

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP on the variation of the terms of the marketing authorisation.