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SCIENCE MEDICINES HEALTH

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Assessment report under article 46

ProQuad

Measles, mumps, rubella and varicella vaccine, live

Procedure no: EMEA/H/C/00622/P046/0038

Note

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



1. Assessment

Introduction

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

Submission of study X06-MMRV-302 in accordance with Article 46 of Regulation (EC) No 1901/2006.

This stand alone study is an open, randomised, comparative, multicentre study to evaluate the immunogenicity and safety of concomitant versus separate administration of a combined measles, mumps, rubella and varicella live vaccine (ProQuad) and a booster dose of Infanrix hexa in healthy children 12 to 23 months of age.

Assessment

In Europe, there are 2 main immunisation schedules for hexavalent vaccines:

1. a primary series with two doses during the first year of life and a booster dose during the second year of life (e.g. in Italy with 2 doses at 3 and 5 months of age plus a booster dose at 11 to 13 months of age); or
2. a primary series of three doses during the first year of life and a booster dose during the second year of life (e.g. in Germany with 3 doses at 2, 3 and 4 months of age plus a booster dose at 11 to 14 months of age).

ProQuad, a combined measles, mumps, rubella and varicella vaccine, should be given to individuals from the age of 12 months onwards. Infants should receive two doses and the second dose should be given at least one month after the second dose.

The purpose of study X06-MMRV-302 was to evaluate the immunogenicity and safety of concomitant versus separate administration of a first dose of ProQuad and a booster dose of Infanrix hexa in healthy children 12 to 23 months of age.

Study design

Study X06-MMRV-302 is an open, randomised, comparative, multicentre phase 3b study and was conducted in 51 study centres in Italy and Germany from January 2007 (FVFS) to March 2008 (LVLS).

In this study 960 subjects were planned to be enrolled. Subjects were randomised in a 2:1:1 ratio to receive:

- Group 1: A first dose of ProQuad concomitantly with a booster dose of Infanrix hexa
- Group 2: A first dose of ProQuad
- Group 3: A booster dose of Infanrix hexa.

Initially, it was planned to have the same number of subjects recruited in Italy and Germany. However, the protocol was amended allowing competitive recruitment between the 2 countries in order to ensure the best recruitment rate and the achievement of the global targeted included population.

Inclusion criteria

Healthy subjects from 12 to 23 months of age (from the 12th month birthday to 1 day prior to the 24th month birthday), without clinical history of measles, mumps, rubella, varicella and zoster, and:

- For Italy, primary vaccination with the combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b vaccine Infanrix hexa as a **2-dose schedule**, with receipt of the second dose ≥ 6 months prior to study vaccination(s),
- For Germany, primary vaccination with the combined diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b vaccine Infanrix hexa as a **3-dose schedule**, with receipt of the third dose ≥ 6 months prior to study vaccination(s).

Exclusion criteria:

Subjects were excluded from the study if they met at least one of the following criteria:

1. Prior receipt of measles, mumps, rubella and/or varicella vaccine either alone or in any combination,
2. Any recent (≤ 30 days) exposure to measles, mumps, rubella, varicella and/or zoster
3. Receipt of any other diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *Haemophilus influenzae* type b containing vaccine (either alone or in any combination) than Infanrix hexa,
4. Any recent (≤ 3 days) history of febrile illness (rectal temperature $\geq 38.0^{\circ}\text{C}$) (100.4°F),
5. Any severe chronic disease,
6. Active untreated tuberculosis,
7. Known personal history of encephalopathy, seizure disorder or progressive, evolving or unstable neurological condition,
8. Any known blood dyscrasia, leukaemia, lymphomas of any type, or other malignant neoplasms affecting the haematopoietic or lymphatic systems,
9. Any severe thrombocytopenia or any other coagulation disorder that would contraindicate intramuscular injection,
10. Prior known sensitivity or allergy to any component of the vaccines including neomycin, sorbitol or gelatin,
11. Any immune impairment, or humoral or cellular deficiency, neoplastic disease or depressed immunity
12. Any recent (≤ 2 days) tuberculin test or scheduled tuberculin test through Visit 2,
13. Any previous (≤ 150 days) receipt of immune serum globulin or any blood-derived products or scheduled to be administered through Visit 2,
14. Any recent (≤ 30 days) receipt of an inactivated or a live non-study vaccine or scheduled non-study vaccination through Visit 2,
15. Any medical condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives,

16. Any recent (= <30 days) participation or scheduled participation in any other clinical trial through Visit 2.

Treatments

Two visits were scheduled during the follow-up period of the study: at Day 0 (Visit 1, vaccination day), and at Day 42 (Visit 2, 42 to 56 days after vaccination). At Visit 1 subjects received either ProQuad concomitantly with Infanrix hexa booster (Group 1) or ProQuad alone (Group 2) or Infanrix hexa booster alone (Group 3). ProQuad had to be injected by sub-cutaneous route of administration and Infanrix hexa had to be injected by intra-muscular route of administration. In Group 1, the injection of ProQuad had to be done in the contra-lateral arm than the one for Infanrix hexa.

The test vaccines were ProQuad batches 652834 and NF56400 and Infanrix hexa batch no A21CA244A.

The three vaccine batches were used in both countries.

The timing of blood samples and the planned immunogenicity evaluation is summarised in table 1.

Table 1. Timing of blood samples and immunogenicity analyses

	Group 1	Group 2	Group 3
	ProQuad+ Infanrix hexa	ProQuad	Infanrix hexa
Timing			
Day 7 to Day 10: Blood sample 1 (BS1)	✓	✓	✓
Day 42 to Day 56: Blood sample 2 (BS2)	✓	✓	✓
Measurement			
Measles, mumps, rubella, varicella	✓	✓	
Hep B, Hib, P, D, T, IPV	✓		✓

Study objectives and hypotheses

The **primary study objective** was to demonstrate that ProQuad can be administered concomitantly with a booster dose of Infanrix hexa to healthy children of 12 to 23 months of age without impairing the antibody response rates to measles, mumps, rubella, varicella, Hep B and *Haemophilus influenzae* type b (Hib), nor to the 3 pertussis antibody titres measured at 42 days following vaccination.

In relation to the primary objective of the study, the following hypotheses were tested.

- The non-inferiority of Group 1 (ProQuad + Infanrix hexa) compared to Group 2 (ProQuad alone) was tested for measles, mumps, rubella and varicella as follows: the Group 1 response rates were considered non-inferior to the Group 2 response rates if, for each valence, the two-sided 95% Confidence Interval (CI) around the difference in response rates (Group 1 – Group 2) excluded a decrease of 10% or more (i.e. the non-inferiority margin),
- The non-inferiority of Group 1 (ProQuad + Infanrix hexa) compared to Group 3 (Infanrix hexa alone) was tested for Hep B and Hib as follows: the Group 1 response rates were considered non-inferior to the Group 3 response rates if, for each valence, the two-sided 95% CI around the difference in response rates (Group 1 – Group 3) excluded a decrease of 5% or more (i.e. the non-inferiority margin),

- The non-inferiority of Group 1 (ProQuad + Infanrix hexa) compared to Group 3 (Infanrix hexa alone) was tested for pertussis (PT, FHA and PRN) as follows: the Group 1 antibody titres were considered non-inferior to the Group 3 antibody titres if, for each valence (PT, FHA and PRN), the two-sided 95% CI around the ratio of post-vaccination GMT (Group 1/Group 3) excluded a decrease of 2-fold or more (i.e. the non-inferiority margin).

Assessor's comment:

The concomitant use of ProQuad and Infanrix hexa is proposed at the time of the first immunisation of the 2-dose schedule of ProQuad and a booster vaccination for Infanrix hexa. Consequently different non-inferiority margins are defined for the response rates against the various antigens. The non-inferiority margin of 10% defined for measles, mumps, rubella and varicella and the margin of 5% for Hep B and Hib are acceptable. Moreover a non-inferiority margin for pertussis excluding a two fold decrease or more is appropriately defined.

The statistical analysis for the demonstration of the non-inferiority of response rates used stratification by region (i.e. centres or pooled centres based on geographic location) with a weight proportional to the number of subjects within each region. The statistical analysis for the demonstration of the non-inferiority of pertussis titres was based on an ANCOVA model with the log-transformed post vaccination titres as response, the log-transformed baseline titres as covariate, the Infanrix hexa primary series schedule, the Region (nested effect) and the Group as fixed effects.

The **secondary study objectives** were

- To describe the antibody titres and the antibody response rates to measles, mumps, rubella, varicella, D, T, P, Hep B, IPV and Hib as measured at 42 days following vaccination when administered to healthy children 12 to 23 months of age, by Infanrix hexa primary vaccination schedule and all data pooled.
- To evaluate the safety profile of ProQuad when administered concomitantly with a booster dose of Infanrix hexa to healthy children 12 to 23 months of age, by Infanrix hexa primary vaccination schedule and all data pooled.

Immunogenicity - secondary objectives analyses

Descriptive statistics were provided by Infanrix hexa primary vaccination schedule and all data pooled for:

- Me, Mu, Ru, Va antibody GMT (and 95% CIs) in Group 1 and Group 2,
- Rates (and 95% CIs) of subjects with varicella antibody titres ≥ 1.25 gpELISA units/mL in subjects seronegative at baseline,
- D, T, and IPV response rates (and 95% CIs) in Group 1 and Group 3,
- D, T, P, Hep B, IPV, and Hib antibody GMT (and 95% CIs) in Group 1 and Group 3,
- Pertussis response rates (and 95% CIs) and GMTR (and 95% CIs) in Group 1 and Group 3.

Safety - secondary objectives analyses

Descriptive statistics were provided by Infanrix hexa primary vaccination schedule and all data pooled for:

- Global safety profile (i.e. injection-site adverse reactions, systemic adverse events and temperature) in all groups,
- Specific safety profile (i.e. rashes of interest and mumps-like illness).

Results

Study subjects and baseline characteristics

Table 2 summarises the disposition of subjects following enrolment and randomisation. In total, 955 subjects were randomised, of whom 945 subjects (99.0%) completed the study. Among the 10 withdrawals from the study 6 subjects were lost to follow-up, 2 subjects had a protocol deviation and 2 subjects withdrew for personal reasons. A total of 728 subjects were included in Germany and 227 in Italy.

Table 2. Disposition of Subjects

	Group 1 ProQuad + Infanrix hexa	Group 2 ProQuad	Group 3 Infanrix hexa	All
N screened	-	-	-	963
N randomised	479	235	241	955
N vaccinated (a)	477 (99.6%)	235 (100%)	240 (99.6%)	952 (99.7%)
- Italy	117 (24.4%)	54 (23.0%)	56 (23.2%)	227 (23.8%)
- Germany	362 (75.6%)	181 (77.0%)	185 (76.8%)	728 (76.2%)
N completed	472 (98.5%)	234 (99.6%)	239 (99.2%)	945 (99.0%)
N withdrawn	7 (1.5%)	1 (0.4%)	2 (0.8%)	10 (1.0%)
Protocol deviation (b)	2 (0.4%)	0	0	2 (0.2%)
Personal reason	0	0	2 (0.8%)	2 (0.2%)
Lost to follow-up	5 (1.0%)	1 (0.4%)	0	6 (0.6%)

Percentages are calculated based on the number of randomised subjects

(a) With at least one vaccine dose

(b) Subject 24002 already got chicken pox

Subject 36007 had already the booster dose of Infanrix hexa

One centre was excluded from analyses due to a major GCP non compliance (non reliability of vaccination history). The centre had randomized 14 subjects, who were not replaced. Therefore the total number of subjects included in the analysis is less than the number of subjects planned to be enrolled in the study.

The analysis sets of subjects defined for the study is shown in Table 3.

The Full Analysis Set (FAS) consisted of 933 subjects (97.7%) in total and the Per Protocol Set (PPS) consisted of 869 subjects (91.0%).

Table 3. Analysis sets

	Group 1 ProQuad® + Infanrix® hexa N=479	Group 2 ProQuad® N=235	Group 3 Infanrix® hexa N=241	All N=955
Full Analysis Set (FAS)	467 (97.5%)	231 (98.3%)	235 (97.5%)	933 (97.7%)
Per Protocol Set (PPS)	436 (91.0%)	218 (92.8%)	215 (89.2%)	869 (91.0%)
PPS for measles	421 (87.9%)	215 (91.5%)		636 (89.1%) (a)
PPS for mumps	427 (89.1%)	212 (90.2%)		639 (89.5%) (a)
PPS for rubella	431 (90.0%)	215 (91.5%)		646 (90.5%) (a)
PPS for varicella	394 (82.3%)	205 (87.2%)		599 (83.9%) (a)

Percentages are calculated on randomised set
(a) Percentage is calculated on randomised subjects in Groups 1 and 2

The three study groups were comparable in terms of age, gender, height, and weight at baseline. The mean (+/-SD) age at vaccination was 13.5 (+/-1.7) months and the gender distribution was 53.1% male and 46.9% female. The results in Italy and Germany were comparable.

Immunogenicity evaluation

Antibody response rates and GMTs to measles, mumps rubella and varicella

The results for antibody response rates to measles, mumps, rubella and varicella at 6 weeks post vaccination and the non-inferiority analysis are summarised in Table 4.

For group 1 (ProQuad + Infanrix hexa) and group 2 (ProQuad alone), the antibody response rates to measles, mumps, rubella and varicella were $\geq 95.1\%$ post dose 1 in the antigen-specific PPS for measles, mumps, rubella and varicella, respectively. Non-inferiority was demonstrated for each component of ProQuad.

Table 4. Antibody response rates to Measles, Mumps, Rubella and Varicella 6 weeks after vaccination of initially seronegative subjects with ProQuad and non-inferiority analysis – (PPS)

	Group 1 ProQuad® + Infanrix® hexa		Group 2 ProQuad®		Estimate of the difference [Group 1 – Group 2]	[95% CI]	Non- inferiority (a)
	N	Number of responders (Response rate) [95% CI]	N	Number of responders (Response rate) [95% CI]			
Measles	421	410 (97.4%) [95.4;98.7]	215	207 (96.3%) [92.8;98.4]	1.14%	[-1.62;4.82]	Yes
Mumps	427	413 (96.7%) [94.6;98.2]	212	209 (98.6%) [95.9;99.7]	-1.83%	[-4.21;1.10]	Yes
Rubella	431	422 (97.9%) [96.1;99.0]	215	213 (99.1%) [96.7;99.9]	-1.20%	[-3.19;1.35]	Yes
Varicella	394	385 (97.7%) [95.7;99.0]	205	195 (95.1%) [91.2;97.6]	2.53%	[-0.41;6.58]	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.

(a) Non-inferiority is achieved since the lower bound of the two-sided 95% CI is greater than -10%.

GMTs to measles, mumps, rubella and varicella were numerically comparable in group 1 and group 2 six weeks after the first dose of ProQuad (Table 5).

Table 5. Table 5: GMTs to measles, mumps, rubella and varicella 6 weeks after vaccination of initially seronegative subjects with ProQuad– PPS

	Group 1 ProQuad® + Infanrix® hexa			Group 2 ProQuad®		
	N	GMT	[95% CI]	N	GMT	[95% CI]
Measles (ELISA mIU/mL)	421	4581	[4148;5061]	215	4056	[3520;4672]
Mumps (ELISA Ab units/mL)	427	116	[107;127]	212	126	[113;139]
Rubella (IU/mL)	431	90	[83;97]	215	90	[81;99]
Varicella (gpELISA units/mL)	394	16.64	[15.61;17.75]	205	15.31	[13.91;16.86]

Assessor's comment:

The response rates to measles, mumps, rubella and varicella were comparable and found to be noninferior whether a first dose of ProQuad was given concomitantly with a booster dose of Infanrix hexa or given alone. Comparable antibody levels were elicited against all live virus components.

Antibody response rates to Hep B and Hib

The results for antibody response rates to Hep B and Hib and the non-inferiority analysis stratified by region are summarised in Table 6.

For group 1 (ProQuad + Infanrix hexa) and group 3 (Infanrix hexa alone), the antibody response rates to Hep B and Hib were $\geq 95.3\%$ 6 weeks after vaccination with Infanrix hexa in the PPS. Non-inferiority was achieved since the lower bound of the two-side 95% CI was greater than 5%.

Table 6. Table 6: Antibody response rates to Hep B and Hib 6 weeks after vaccination with Infanrix hexa and non-inferiority analysis – PPS

	Group 1 ProQuad® + Infanrix® hexa		Group 3 Infanrix® hexa		Estimate of the difference [Group 1 – Group 3]	[95% CI]	Non- inferiority (a)
	N	Number of responders (Response rate) [95% CI]	N	Number of responders (Response rate) [95% CI]			
Hepatitis B	411	409 (99.5%) [98.3;99.9]	215	211 (98.1%) [95.3;99.5]	1.36%	[-0.29;4.24]	Yes
<i>Haemophilus influenzae</i> type b	387	380 (98.2%) [96.3;99.3]	211	201 (95.3%) [91.5;97.7]	2.97%	[0.17;6.89]	Yes

Response rates were defined as:

- Hepatitis B antibody titre ≥ 10 IU/mL.
- *Haemophilus influenzae* type b antibody titre ≥ 1 μ g/mL.

(a) Non-inferiority is achieved since the lower bound of the two-sided 95% CI is greater than -5%.

It should be noted that the response rates for Hib in Germany (3+1 schedule) following the administration of Infanrix hexa alone (94.5%) was numerically lower compared to ProQuad + Infanrix hexa (98.7%), resulting in a rate difference [95% CI] of 3.89% [0.64; 8.67] in Germany (Table 7). In contrast the two groups were comparable in Italy.

Table 7. Table 7: Estimates of antibody response rates differences between groups to Hep B and Hib 6 weeks after vaccination to Infanrix hexa by Infanrix hexa primary vaccination – PPS

		Group 1 ProQuad® + Infanrix® hexa		Group 3 Infanrix® hexa		Estimate of the difference [Group 1 – Group 3]	[95% CI]
		N	Number of responders (Response rate) [95% CI]	N	Number of responders (Response rate) [95% CI]		
Hepatitis B	Italy	92	92 (100%) [96.1;100]	51	51 (100%) [93.0;100]	0.00%	[-4.04;7.05]
	Germany	319	317 (99.4%) [97.8;99.9]	164	160 (97.6%) [93.9;99.3]	1.81%	[-0.29;5.53]
<i>Haemophilus influenzae</i> type b	Italy	80	78 (97.5%) [91.3;99.7]	48	47 (97.9%) [88.9;99.9]	-0.42%	[-6.95;8.65]
	Germany	307	302 (98.7%) [96.2;99.5]	163	154 (94.5%) [89.8;97.4]	3.89%	[0.64;8.67]

Response rates were defined as:

- Hepatitis B antibody titre ≥ 10 IU/mL.
- *Haemophilus influenzae* type b antibody titre ≥ 1 μ g/mL.

Italy: 2-dose schedule Infanrix® hexa primary vaccination

Germany: 3-dose schedule Infanrix® hexa primary vaccination

Assessor's comment:

Like in other studies evaluating the concomitant administration of Infanrix hexa with a second childhood vaccine (e.g. pneumococcal vaccine) the 4th dose of Infanrix hexa was found to elicit a stronger antibody response against Hib antigens when given concomitantly. This difference was not seen for prior doses and might explain the differences seen here as well between the German (4th dose) and the Italian (3rd dose) subjects. As a higher titre is not considered a clinical issue, this observation needs not to be followed up.

GMT for pertussis

The post-vaccination GMT for pertussis are summarised in Table 8 as well as the non-inferiority analysis adjusted for pre-vaccination titres, Infanrix hexa primary vaccination and region.

For Group 1 (ProQuad + Infanrix hexa) and Group 3 (Infanrix hexa alone), the postvaccination GMT for the 3 pertussis antigens (PT, FHA, and PRN) were comparable and non-inferiority was shown.

Table 8. Table 8: Summary and non-inferiority analysis (adjusted for pre-vaccination titres, Infanrix hexa primary vaccination and region) of antibody titres to pertussis 6 weeks after vaccination with Infanrix hexa – PPS

	Group 1 ProQuad® + Infanrix® hexa		Group 3 Infanrix® hexa		Estimate of the GMT ratio [Group 1 / Group 3]	[95% CI]	Non- inferiority (a)
	N	GMT [95% CI]	N	GMT [95% CI]			
Anti-PT	379	132.6 [123.8;142.0]	209	139.1 [126.7;152.8]	0.97	[0.88;1.08]	Yes
Anti-FHA	386	210.9 [195.7;227.2]	211	189.9 [170.2;211.8]	1.09	[0.98;1.23]	Yes
Anti-PRN	385	310.0 [282.2;340.7]	211	259.7 [226.3;298.1]	1.18	[1.03;1.36]	Yes

(a) Non-inferiority is achieved since the lower bound of the two-sided 95% CI is greater than 0.5.

Of note is the difference in GMTs in Italy and Germany. In Germany the anti-PRN and anti FHA GMT were numerically lower following the administration of Infanrix hexa alone than after concomitant administration, while comparable titres were observed in Italy (Table 9).

Table 9. Table 9: Estimates of GMT ratio (non-adjusted ANOVA model) to pertussis 6 weeks after vaccination with Infanrix hexa by Infanrix hexa primary vaccination– PPS

		Group 1 ProQuad® + Infanrix® hexa		Group 3 Infanrix® hexa		Estimate of the GMT ratio [Group 1 / Group 3]	[95% CI]
		N	GMT [95% CI]	N	GMT [95% CI]		
Anti-FHA	Italy	79	254.6 [215.4;300.9]	48	239.3 [194.7;294.2]	1.06	[0.82;1.39]
	Germany	307	200.9 [184.9;218.3]	163	177.3 [156.1;201.4]	1.13	[0.98;1.31]
Anti-PRN	Italy	78	318.4 [268.0;378.2]	48	306.0 [240.1;389.9]	1.04	[0.78;1.39]
	Germany	307	307.9 [275.8; 343.8]	163	247.5 [210.1;291.6]	1.24	[1.03;1.51]

Italy: 2-dose schedule Infanrix® hexa primary vaccination
Germany: 3-dose schedule Infanrix® hexa primary vaccination

Assessor's comment:

The primary objectives of this study were met. Concomitant administration of the first dose of ProQuad with a booster dose of Infanrix hexa elicits an immune response against measles, mumps, rubella, varicella, HepB, Hib and pertussis that is noninferior to the administration of ProQuad or Infanrix hexa alone. The results of the FAS were comparable to those on the PPS.

In general higher antibody titers and response rates were observed following concomitant administration compared to administration of the vaccines alone indicating that there is no negative immunological interference following concomitant administration of these two vaccines.

Response rates and antibody GMT for diphtheria, tetanus and poliomyelitis types 1, 2, and 3

The response rates at 6 weeks post-vaccination for diphtheria, tetanus and poliomyelitis types 1, 2 and 3 in group 1 and group 3 were numerically comparable for the PPS and they were comparable for both immunisation schedules routinely used in Italy and Germany.

Seroprotection rates increased similarly following vaccination in both Group 1 and Group 3:

- For diphtheria (titre ≥ 0.1 IU/mL) from 59 - 62% prevaccination to $\geq 99.7\%$ postvaccination
- For tetanus, (titre ≥ 0.1 IU/mL) from 93 - 94% prevaccination to 100% postvaccination
- For poliomyelitis types 1, 2 and 3 (titre ≥ 8 (1/dil) from 94 - 97% prevaccination to $\geq 99.5\%$ postvaccination.

Assessor's comment:

The response rates and antibody titres for diphtheria, tetanus and polio virus type 1, 2 and 3 were comparable in both groups and reached nearly 100% for all components.

Safety evaluation

The following safety evaluation does not include site 32, because data from site 32 have been excluded due to fraud.

Among the 955 randomised subjects, 8 were not part of the Safety Analysis Set because they were not vaccinated at all (n=3) or withdrew prematurely before providing any safety information (n=5, subjects 07012, 34001 and 34005 in Group 1, 21019 in Group 2 and 14034 in Group 3). Therefore the Safety Analysis Set consisted of 947 subjects (99.2%). An overview of the subjects, who received the vaccines, is given in table 10.

Table 10. Table 10: Overview of randomized subjects

	Group 1 ProQuad® + Infanrix® hexa (N=479)	Group 2 ProQuad® (N=235)	Group 3 Infanrix® hexa (N=241)	All (N=955)
N vaccinated	477 (99.6%)	235 (100%)	240 (99.6%)	952 (99.7%)
ProQuad® injection done	477 (100%)	234 (99.6%)	1 (0.4%)	712 (74.8%)
Full dose	477 (100%)	234 (100%)	1 (100%)	712 (100%)
Infanrix® hexa injection done	477 (100%)	1 (0.4%)	239 (99.6%)	717 (75.3%)
Full dose	476 (99.8%) (1)	1 (100%)	239 (100%)	716 (99.9%)

(1) Subject 04054 did not receive a full dose because the reconstitution of the Hib powder with the D-T-aP-HBs-IPV suspension was not done

There were 2 errors regarding vaccination schedule not respecting randomisation affecting the safety analysis:

- Subject 42001 was randomised in Group 3 but vaccinated according to Group 2 schedule and was analysed for safety according to actual vaccination (i.e., in Group 2).
- Subject 51001 was randomised in Group 2 but vaccinated according to Group 3 schedule and was analysed for safety according to actual route (i.e., in Group 3).

Consequently, the Safety Analyses Sets consisted of 474 subjects in Group 1, 234 subjects in Group 2 and 239 subjects in Group 3.

A summary of the safety measurements performed in the study is presented in table 11.

Table 11. Table 11: Safety measurement and timing

	Visit 1			Visit 2
	Day 0	Day 4	Day 28	Day 42 to 56
Vaccination				
Group 1	ProQuad®+Infanrix® hexa			
Group 2	ProQuad®			
Group 3	Infanrix® hexa			
	Solicited injection-site adverse reactions (1)			
	Unsolicited (2) injection-site adverse reactions			
	Measles-like rashes, mumps-like symptoms, rubella-like rashes, varicella-like rashes and/or zoster-like rashes			
	Daily temperature (3)			
	Unsolicited (4) systemic adverse events			
	Serious adverse events			
(1) Injection-site erythema, injection-site swelling and injection-site pain				
(2) Spontaneously reported reactions. Could include injection-site erythema, injection-site swelling and injection-site pain starting from Day 5 to Day 28				
(3) Daily axillary temperature and rectal temperature when axillary temperature was $\geq 37.1^{\circ}\text{C}$ (98.8°F)				
(4) Spontaneously reported events				

Intensity of an adverse event

For injection-site adverse reactions and systemic adverse events, intensity was:

- For measurable injection-site adverse reactions, the maximum largest diameter in cm.

The 4 classes of measurable lesions were defined as follows: ≤ 2.5 cm, 2.5–5.0 cm, 5.0–7.5 cm, > 7.5 cm

- For systemic adverse events and non-measurable injection-site reactions, the maximum intensity observed:
 - mild: awareness of sign and symptom but easily tolerated
 - moderate: definitely acting like something is wrong
 - severe: extremely distressed or unable to do usual activity.
- For fever, the highest observed temperature measured in degrees Celsius.
- *Measles-, rubella-, varicella- and zoster-like rashes and mumps-like symptoms*

In case of measles-, rubella-, varicella- or zoster-like rashes (injection-site or non-injection site) or in case of symptoms resembling mumps occurring from Day 0 to Day 28, as described in the Diary Card, the parent(s) or legal representative were instructed to immediately contact the investigator. In this event, the subject was examined by the investigator as soon as possible but no later than 72 hours (i.e. 3 days) following the onset of the symptoms.

Rashes were recorded on module "Rashes" of the Diary Cards. The clinical findings and the subject's history of exposure to measles, mumps, rubella, varicella and/or zoster were documented directly by the investigator into the e-CRF and in the subject's source document.

Mumps-like symptoms like swollen parotid were recorded as a systemic adverse event.

Immediate systemic adverse events (i.e. occurring in the first 20 minutes following vaccination) were recorded directly by the investigator into the e-CRF and in the subject's source document.

Systemic adverse events occurring from Day 0 (20 minutes following vaccination) to Day 28 were recorded in the Diary Card. Systemic adverse events were all spontaneously reported.

Adverse events and serious adverse events (e.g. hospitalisation) and visits to a physician occurring from Day 0 to Visit 2 were recorded in the Diary Card, either as an injection-site adverse reaction or as a systemic adverse event.

Assessor's comment:

Study X06-MMRV-302 was well designed and well conducted. Around 99.2 % of the children continued the study till the end, which is a high percentage for this age group.

Safety Results:

Thus, the Safety Analysis Set consisted of 947 subjects, including 474 subjects in group 1, 234 subjects in group 2 and 239 subjects in group 3.

Overall, 90.5%, 72.6% and 84.1% of subjects reported at least one injection-site adverse reaction or systemic adverse event from Day 0 to Day 28 after vaccination, in group 1 (Infanrix hexa + ProQuad), group 2 (ProQuad alone) and group 3 (Infanrix hexa alone), respectively.

A global summary of safety is given in tables 12, 13 and 14.

Within the observation period from Day 0 to Day 28 a comparable percentage of subjects reported at least one injection-site adverse reaction or systemic adverse event related to Infanrix hexa (Table 12). In group 1 (ProQuad + Infanrix hexa) 71.9% reported adverse reactions and in group 3 (Infanrix hexa alone) 69.5% of subjects experienced adverse reaction. In contrast, more subjects reported injection-site adverse reaction or systemic adverse event related to ProQuad in group 1 (ProQuad + Infanrix hexa) compared to Group 2 (ProQuad alone) (54.4% and 46.6%, respectively).

Table 12. Global summary of safety – part 1

	Group 1 ProQuad® + Infanrix® hexa (N=474)	Group 2 ProQuad® (N=234)	Group 3 Infanrix® hexa (N=239)
	Nb subj (%)	Nb subj (%)	Nb subj (%)
Injection-site adverse reaction / systemic adverse event from Day 0 to Day 28	429 (90.5%)	170 (72.6%)	201 (84.1%)
Injection-site adverse reaction / systemic adverse event related to ProQuad® from Day 0 to Day 28	258 (54.4%)	109 (46.6%)	-
Injection-site adverse reaction / systemic adverse event related to Infanrix® hexa from Day 0 to Day 28	341 (71.9%)	-	166 (69.5%)
Injection-site adverse reaction from Day 0 to Day 28	348 (73.4%)	62 (26.5%)	156 (65.3%)
Injection-site adverse reaction to ProQuad® from Day 0 to Day 28	172 (36.3%)	62 (26.5%)	-

Assessor's comment

The data indicate that solicited injection site reactions are mainly caused by the vaccine Infanrix hexa.

As shown in table 13 solicited injection site adverse reactions (erythema, pain and swelling) to ProQuad from Day 0 to Day 4 were reported by more subjects in Group 1 compared to Group 2 (31.6% and 19.7%, respectively), while those to Infanrix hexa were reported by a comparable number of subjects in Group 1 and Group 3 (65.4% and 65.3%).

From Day 0 to Day 28, a comparable proportion of subjects experienced unsolicited injection site adverse reactions to ProQuad (8.2% in Group 1 and 9.0% in Group 2) and to Infanrix hexa (5.7% in Group 1 and 3.3% in Group 3).

From Day 0 to Day 28 a comparable proportion of subjects in each group reported systemic adverse events related to ProQuad (32.1% in Group 1 and 29.5% in Group 2) and related to Infanrix hexa (21.1% in Group 1 and 16.7% in Group 3).

From Day 0 to Day 28, injection-site rashes of interest were reported by 3.0% of subjects in Group 1, 4.3% in Group 2 and 0.8% in Group 3.

A total of 64 (13.5%) and 24 (10.3%) subjects reported non-injection-site rashes of interest in Group 1 and Group 2, respectively. Neither mumps nor mumps-like illness was reported in this study (Table 13).

Table 13. Global summary of safety - part 2

	Group 1 ProQuad® + Infanrix® hexa (N=474)	Group 2 ProQuad® (N=234)	Group 3 Infanrix® hexa (N=239)
	Nb subj (%)	Nb subj (%)	Nb subj (%)
Solicited injection-site adverse reaction to ProQuad® from Day 0 to Day 4	150 (31.6%)	46 (19.7%)	-
Injection-site erythema to ProQuad® from Day 0 to Day 4	79 (16.7)	25 (10.7)	-
Injection-site pain to ProQuad® from Day 0 to Day 4	99 (20.9)	33 (14.1)	-
Injection-site swelling to ProQuad® from Day 0 to Day 4	46 (9.7)	6 (2.6)	-
Unsolicited injection-site adverse reaction to ProQuad® from Day 0 to Day 28	39 (8.2%)	21 (9.0%)	-
Injection-site adverse reaction to Infanrix® hexa from Day 0 to Day 28	312 (65.8%)	-	156 (65.3%)
Solicited injection-site adverse reaction to Infanrix® hexa from Day 0 to Day 4	310 (65.4%)	-	156 (65.3%)
Injection-site erythema to Infanrix® hexa from Day 0 to Day 4	236 (49.8)	-	126 (52.7)
Injection-site pain to Infanrix® hexa from Day 0 to Day 4	185 (39.0)	-	84 (35.1)
Injection-site swelling to Infanrix® hexa from Day 0 to Day 4	180 (38.0)	-	93 (38.9)
Unsolicited injection-site adverse reaction to Infanrix® hexa from Day 0 to Day 28	27 (5.7%)	-	8 (3.3%)
Systemic adverse event from Day 0 to Day 28	332 (70.0%)	152 (65.0%)	149 (62.3%)
Systemic adverse event related to ProQuad® from Day 0 to Day 28	152 (32.1%)	69 (29.5%)	-
Systemic adverse event related to Infanrix® hexa from Day 0 to Day 28	100 (21.1%)	-	40 (16.7%)
Injection-site rash of interest from Day 0 to Day 28	14 (3.0%)	10 (4.3%)	2 (0.8%)
Non-injection site rash of interest from Day 0 to Day 28	64 (13.5%)	24 (10.3%)	9 (3.8%)
Measles / non-injection site measles-like rash from Day 0 to Day 28	33 (7.0%)	16 (6.8%)	5 (2.1%)
Rubella / non-injection site rubella-like rash from Day 0 to Day 28	18 (3.8%)	6 (2.6%)	1 (0.4%)
Varicella / non-injection site varicella-like rash from Day 0 to Day 28	15 (3.2%)	2 (0.9%)	3 (1.3%)
Herpes zoster / non-injection site herpes zoster-like rash from Day 0 to Day 28	1 (0.2%)	1 (0.4%)	0
Mumps / mumps-like illness from Day 0 to Day 28	0	0	0

Overall, 69.3%, 61.1%, and 57.3% of subjects reported body temperature (rectal or equivalent) $\geq 38^{\circ}\text{C}$ within 28 days after vaccination in Groups 1, 2, and 3, respectively. The corresponding number of subjects reporting body temperature $\geq 39.4^{\circ}\text{C}$ were 22.6%, 20.5% and 15.9% (Table 14).

Table 14. Global summary of safety - part 3

	Group 1 ProQuad® + Infanrix® hexa (N=474)	Group 2 ProQuad® (N=234)	Group 3 Infanrix® hexa (N=239)
	Nb subj (%)	Nb subj (%)	Nb subj (%)
At least one rectal (or equivalent) temperature from Day 0 to Day 28 \geq38.0°C	328 (69.3%)	143 (61.1%)	137 (57.3%)
At least one rectal (or equivalent) temperature from Day 0 to Day 28 \geq 39.4 °C	107 (22.6%)	48 (20.5%)	38 (15.9%)
Serious adverse event from Day 0 to Visit 2	7 (1.5%)	6 (2.6%)	4 (1.7%)
Serious adverse event related to ProQuad® from Day 0 to Visit 2	0	0	-
Serious adverse event related to Infanrix® hexa from Day 0 to Visit 2	0	-	0
Death from Day 0 to Visit 2	0	0	0
Withdrawal for adverse event from Day 0 to Visit 2	0	0	0

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

Assessor's Comment:

Number of systemic reactions including high body temperature were comparable in all three treatment groups, thus, concomitant use of ProQuad with Infanrix hexa does not seem to raise any safety concerns. In regards to local reactions (pain, erythema and swelling) a clear trend of higher reactogenicity is seen in the concomitant administration in comparison to the single administration of ProQuad. Comparing the local reactions in regards to concomitant administration and single administration of Infanrix hexa the percentage of reactogenicity is comparable in both treatment groups.

Serious adverse events between Day 0 and Visit 2

From Day 0 to Visit 2, a total of 19 serious adverse events were reported by 17 subjects. Eight serious adverse events were reported by 7 subjects (1.5%) in Group 1, 7 serious adverse events were reported by 6 subjects (2.6%) in Group 2, and 4 serious adverse events were reported by 4 subjects (1.7%) in Group 3 (Table 15).

Of note, 2 febrile convulsions were reported in Group 1, one occurred 2 days after vaccination and was associated with serious otitis media and nonserious upper respiratory tract infection and the other occurred 33 days after vaccination, and was associated with non-serious upper respiratory tract infection. In the Investigator's opinion, none of these serious adverse events was related to either ProQuad or Infanrix hexa.

No subject has been withdrawn from the study due to an adverse event. No subjects died during the course of the study.

Table 15. Summary of serious adverse events

	Group 1 (N=474)						Group 2 (N=234)				Group 3 (N=239)			
	All		Related to ProQuad®		Related to Infanrix® hexa		All		Related to ProQuad®		All		Related to Infanrix® hexa	
	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)
Serious adverse event	8	7 (1.5%)	0	0 (0.0%)	0	0 (0.0%)	7	6 (2.6%)	0	0 (0.0%)	4	4 (1.7%)	0	0 (0.0%)
INFECTIONS AND INFESTATIONS	6	6 (1.3%)	0	0 (0.0%)	0	0 (0.0%)	7	6 (2.6%)	0	0 (0.0%)	3	3 (1.3%)	0	0 (0.0%)
Bronchitis	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	3	3 (1.3%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)
Bronchopneumonia	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Conjunctivitis bacterial	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Gastroenteritis	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Gastroenteritis rotavirus	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)
Influenza	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)
Otitis media	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Upper respiratory tract infection	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Urinary tract infection	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Viral upper respiratory tract infection	1	1 (0.2%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)

	Group 1 (N=474)						Group 2 (N=234)				Group 3 (N=239)			
	All		Related to ProQuad®		Related to Infanrix® hexa		All		Related to ProQuad®		All		Related to Infanrix® hexa	
	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)	Nb AEs	Nb Subj(%)
Electric shock	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (0.4%)	0	0 (0.0%)
NERVOUS SYSTEM DISORDERS	2	2 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Febrile convulsion	2	2 (0.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)

Nb AEs: number of episodes of the considered event
Nb subj: number of subjects presenting at least once the considered event
%: percentage of subjects presenting at least once the considered event; percentages are calculated regarding the Safety Analysis Set

Summary of injection-site adverse reactions

Within the diary cards the parents had to fill in all observations due to injection site reactions, which were subdivided into parts of solicited and unsolicited injection site reactions. Injection site adverse reactions were split by the different arms for the concomitant group. Table 16 summarises the injection site adverse reactions.

Injection site adverse reactions to ProQuad:

From Day 0 to Day 28 after vaccination, more subjects reported at least one injection-site adverse reaction related to ProQuad in Group 1 (ProQuad + Infanrix hexa) compared to Group 2 (ProQuad alone) (36.3% and 26.5%, respectively). This difference between Group 1 and Group 2 was mainly due to the solicited injection-site adverse reactions to ProQuad from Day 0 to Day 4, which were reported by 31.6% of subjects in Group 1 and 19.7% in Group 2. Each of the 3 solicited injection-site adverse reaction contributed to this difference: injection-site erythema (16.7% versus 10.7%), injection-site pain (20.9% versus 14.1%), and injection-site swelling (9.7% versus 2.6%).

Overall, a comparable proportion of subjects experienced unsolicited injection-site adverse reactions to ProQuad from Day 0 to Day 28 in Group 1 and Group 2 (8.2% and 9.0%, respectively). The intensity of injection-site adverse reactions reported from Day 0 to Day 28 were mainly mild and with a low percentage severe (e.g. 0.2% for erythema and pain as well as 0.4% for swelling) in Group 1. In Group 2 (ProQuad alone) no severe injection site adverse event was reported.

Table 16. Summary of Injection-Site Adverse Reactions to ProQuad from Day 0 to Day 28

	Group 1 ProQuad® + Infanrix® hexa (N=474) Nb subj (%)	Group 2 ProQuad® (N=234) Nb subj (%)
Injection-site adverse reaction from Day 0 to Day 28	172 (36.3%)	62 (26.5%)
Solicited injection-site adverse reaction from Day 0 to Day 4	150 (31.6%)	46 (19.7%)
Injection-site erythema	79 (16.7%)	25 (10.7%)
Injection-site pain	99 (20.9%)	33 (14.1%)
Injection-site swelling	46 (9.7%)	6 (2.6%)
Unsolicited injection-site adverse reaction from Day 0 to Day 28	39 (8.2%)	21 (9.0%)
Injection-site bruising	2 (0.4%)	0
Injection-site dryness	0	1 (0.4%)
Injection-site erythema	18 (3.8%)	6 (2.6%)
Injection-site hematoma	2 (0.4%)	3 (1.3%)
Injection-site induration	2 (0.4%)	1 (0.4%)
Injection-site nodule	1 (0.2%)	0
Injection-site papule	0	1 (0.4%)
Injection-site pustule	2 (0.4%)	0
Injection-site rash	13 (2.7%)	10 (4.3%)
Injection-site swelling	4 (0.8%)	1 (0.4%)
Injection-site warmth	1 (0.2%)	0

Nb subj (%): number (percentage) of subjects presenting at least once the considered event.

Note: unsolicited injection-site adverse reactions, sorted by MedDRA preferred term, may include injection-site erythema, injection-site swelling and injection-site pain occurring from Day 5 to Day 28.

Injection site adverse reactions to Infanrix hexa:

As shown in table 17, a comparable proportion of subjects reported injection-site adverse reactions to Infanrix hexa in Group 1 (ProQuad + Infanrix hexa) compared to Group 3 (Infanrix hexa alone) (65.8% and 65.3%, respectively). Indeed, a comparable proportion of subjects experienced solicited injection-site adverse reactions to Infanrix hexa from Day 0 to Day 4 (65.4% in Group 1 and 65.3% in Group 3), including injection-site erythema (49.8% and 52.7%, respectively), injection-site pain (39.0% and 35.1%) and injection-site swelling (38.0% and 38.9%).

Overall, a comparable proportion of subjects experienced unsolicited injection-site adverse reactions to Infanrix hexa from Day 0 to Day 28 in Group 1 and Group 3 (5.7% and 3.3%, respectively).

Regarding the intensity of the injection site reaction caused by Infanrix hexa the percentage of severe solicited reactions is comparable in the concomitant group versus the single application of Infanrix hexa (e.g. erythema [2.7% vs 1.7%], pain [1.5% vs 3.3%] and swelling [1.9% vs 0.8%]). The percentage of unsolicited injection-site reactions was slightly increased in the concomitant group compared to the Infanrix hexa group. Unsolicited injection-site pain (after Day 4) of severe intensity was reported by one subject (0.2%) in Group 1. No unsolicited injection-site reaction of severe intensity was reported by subjects in Group 3.

Table 17. Summary of Injection-Site Adverse Reactions to Infanrix hexa from Day 0 to Day 28

	Group 1 ProQuad® + Infanrix® hexa (N=474) Nb subj (%)	Group 3 Infanrix® hexa (N=239) Nb subj (%)
Injection-site adverse reaction from Day 0 to Day 28	312 (65.8%)	156 (65.3%)
Solicited injection-site adverse reaction from Day 0 to Day 4	310 (65.4%)	156 (65.3%)
Injection site erythema	236 (49.8%)	126 (52.7%)
Injection site pain	185 (39.0%)	84 (35.1%)
Injection site swelling	180 (38.0%)	93 (38.9%)
Unsolicited injection-site adverse reaction from Day 0 and to 28	27 (5.7%)	8 (3.3%)
Injection site erythema	3 (0.6%)	0
Injection site haemorrhage	1 (0.2%)	0
Injection site hematoma	5 (1.1%)	1 (0.4%)
Injection site hypersensitivity	0	1 (0.4%)
Injection site induration	10 (2.1%)	4 (1.7%)
Injection site pain	1 (0.2%)	0
Injection site pruritus	1 (0.2%)	0
Injection site rash	1 (0.2%)	2 (0.8%)
Injection site reaction	1 (0.2%)	0
Injection site swelling	2 (0.4%)	0
Injection site warmth	6 (1.3%)	2 (0.8%)

Nb subj (%): number (percentage) of subjects presenting at least once the considered event.
Note: unsolicited injection-site adverse reactions, sorted by MedDRA preferred term, may include injection-site erythema, injection-site swelling and injection-site pain occurring from Day 5 to Day 28.

Summary of systemic reactions

Overall, the percentage of subjects with at least one systemic adverse event reported from Day 0 to Day 28 was comparable between groups (70.0% in Group 1, 65.0% in Group 2 and 62.3% in Group 3) as given in Table 18.

Table 18. Summary of Systemic Adverse Events (Incidence $\geq 1\%$) From Day 0 to Day 28

Systemic adverse events presented by SOC	Group 1 ProQuad® + Infanrix® hexa (N=474)			Group 2 ProQuad® (N=234)		Group 3 Infanrix® hexa (N=239)	
	All	Related to ProQuad®	Related to Infanrix® hexa	All	Related to ProQuad®	All	Related to Infanrix® hexa
	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)
Systemic adverse events from Day 0 to Day 28	332 (70.0%)	152 (32.1%)	100 (21.1%)	152 (65.0%)	69 (29.5%)	149 (62.3%)	40 (16.7%)
EYE DISORDERS	9 (1.9%)	0	0	6 (2.6%)	1 (0.4%)	4 (1.7%)	0
Conjunctivitis	9 (1.9%)	0	0	6 (2.6%)	1 (0.4%)	4 (1.7%)	0
GASTROINTESTINAL DISORDERS	58 (12.2%)	3 (0.6%)	4 (0.8%)	29 (12.4%)	1 (0.4%)	34 (14.2%)	7 (2.9%)
Constipation	1 (0.2%)	0	0	3 (1.3%)	0	1 (0.4%)	0
Diarrhoea	22 (4.6%)	2 (0.4%)	2 (0.4%)	14 (6.0%)	1 (0.4%)	14 (5.9%)	2 (0.8%)
Enteritis	10 (2.1%)	1 (0.2%)	1 (0.2%)	2 (0.9%)	0	5 (2.1%)	2 (0.8%)
Teething	14 (3.0%)	0	0	9 (3.8%)	0	6 (2.5%)	0
Vomiting	14 (3.0%)	0	1 (0.2%)	2 (0.9%)	0	14 (5.9%)	5 (2.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	193 (40.7%)	118 (24.9%)	81 (17.1%)	84 (35.9%)	54 (23.1%)	72 (30.1%)	30 (12.6%)
Irritability	7 (1.5%)	5 (1.1%)	6 (1.3%)	3 (1.3%)	3 (1.3%)	3 (1.3%)	3 (1.3%)
Pyrexia	184 (38.8%)	114 (24.1%)	76 (16.0%)	80 (34.2%)	50 (21.4%)	68 (28.5%)	27 (11.3%)
INFECTIONS AND INFESTATIONS	154 (32.5%)	8 (1.7%)	4 (0.8%)	76 (32.5%)	5 (2.1%)	73 (30.5%)	1 (0.4%)
Bronchitis	27 (5.7%)	2 (0.4%)	1 (0.2%)	15 (6.4%)	2 (0.9%)	12 (5.0%)	0
Ear infection	2 (0.4%)	0	0	3 (1.3%)	0	1 (0.4%)	0
Exanthema subitum	5 (1.1%)	1 (0.2%)	0	2 (0.9%)	0	2 (0.8%)	0
Gastroenteritis	17 (3.6%)	1 (0.2%)	1 (0.2%)	4 (1.7%)	0	4 (1.7%)	0
Influenza	6 (1.3%)	1 (0.2%)	1 (0.2%)	7 (3.0%)	0	6 (2.5%)	0
Nasopharyngitis	48 (10.1%)	1 (0.2%)	0	14 (6.0%)	2 (0.9%)	18 (7.5%)	0
Otitis media	10 (2.1%)	0	1 (0.2%)	4 (1.7%)	0	2 (0.8%)	0
Pharyngitis	3 (0.6%)	0	0	4 (1.7%)	0	4 (1.7%)	1 (0.4%)
Respiratory tract infection	5 (1.1%)	0	0	3 (1.3%)	0	1 (0.4%)	0
Rhinitis	27 (5.7%)	2 (0.4%)	0	20 (8.5%)	1 (0.4%)	9 (3.8%)	0
Tonsillitis	6 (1.3%)	0	0	0	0	5 (2.1%)	0
Upper respiratory tract infection	14 (3.0%)	0	0	9 (3.8%)	0	7 (2.9%)	0
Viral infection	4 (0.8%)	0	0	3 (1.3%)	0	5 (2.1%)	0

Systemic adverse events presented by SOC	Group 1 ProQuad® + Infanrix® hexa (N=474)			Group 2 ProQuad® (N=234)		Group 3 Infanrix® hexa (N=239)	
	All	Related to ProQuad®	Related to Infanrix® hexa	All	Related to ProQuad®	All	Related to Infanrix® hexa
	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)	Nb Subj (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (1.3%)	0	0	4 (1.7%)	0	11 (4.6%)	0
Arthropod bite	1 (0.2%)	0	0	1 (0.4%)	0	3 (1.3%)	0
Head injury	3 (0.6%)	0	0	0	0	5 (2.1%)	0
METABOLISM AND NUTRITION DISORDERS	5 (1.1%)	1 (0.2%)	1 (0.2%)	6 (2.6%)	3 (1.3%)	3 (1.3%)	1 (0.4%)
Anorexia	3 (0.6%)	1 (0.2%)	1 (0.2%)	3 (1.3%)	1 (0.4%)	2 (0.8%)	0
PSYCHIATRIC DISORDERS	17 (3.6%)	4 (0.8%)	7 (1.5%)	7 (3.0%)	2 (0.9%)	2 (0.8%)	1 (0.4%)
Crying	3 (0.6%)	2 (0.4%)	2 (0.4%)	3 (1.3%)	1 (0.4%)	0	0
Restlessness	10 (2.1%)	1 (0.2%)	4 (0.8%)	3 (1.3%)	1 (0.4%)	2 (0.8%)	1 (0.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	35 (7.4%)	2 (0.4%)	1 (0.2%)	16 (6.8%)	1 (0.4%)	13 (5.4%)	0
Cough	31 (6.5%)	2 (0.4%)	1 (0.2%)	13 (5.6%)	1 (0.4%)	11 (4.6%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	105 (22.2%)	44 (9.3%)	9 (1.9%)	37 (15.8%)	19 (8.1%)	35 (14.6%)	7 (2.9%)
Dermatitis	7 (1.5%)	0	0	1 (0.4%)	0	4 (1.7%)	1 (0.4%)
Dermatitis diaper	20 (4.2%)	0	0	6 (2.6%)	0	10 (4.2%)	0
Eczema	9 (1.9%)	1 (0.2%)	1 (0.2%)	2 (0.9%)	0	1 (0.4%)	0
Erythema	5 (1.1%)	1 (0.2%)	0	0	0	1 (0.4%)	0
Rash	7 (1.5%)	0	0	4 (1.7%)	1 (0.4%)	2 (0.8%)	0
Rash morbilliform	33 (7.0%)	22 (4.6%)	2 (0.4%)	16 (6.8%)	13 (5.6%)	5 (2.1%)	3 (1.3%)
Rash rubelliform	17 (3.6%)	12 (2.5%)	2 (0.4%)	6 (2.6%)	5 (2.1%)	1 (0.4%)	1 (0.4%)
Rash vesicular	14 (3.0%)	7 (1.5%)	2 (0.4%)	3 (1.3%)	1 (0.4%)	3 (1.3%)	0

A comparable percentage of subjects in each group reported systemic adverse events related to ProQuad from Day 0 to Day 28 (32.1% in Group 1 and 29.5% in Group 2) as well as to Infanrix hexa (21.1% in Group 1 and 16.7% in Group 3).

- The more frequently systemic adverse events reported as related to ProQuad by $\geq 1\%$ of subjects were pyrexia (24.1% in Group 1 and 21.4% in Group 2), rash morbilliform (4.6% in Group 1 and 5.6% in Group 2), rash rubelliform (2.5% in Group 1 and 2.1% in Group 2), rash vesicular (1.5% in Group 1 and 0.4% in Group 2) and irritability (1.1% in Group 1 and 1.3% in Group 2).
- The more frequently systemic adverse events reported as related to Infanrix hexa by $\geq 1\%$ of subjects were pyrexia (16.0% in Group 1 and 11.3% in Group 3), vomiting (0.2% in Group 1 and 2.1% in Group 3), irritability (1.3% in both groups) and rash morbilliform (0.4% in Group 1 and 1.3% in Group 3).

Regarding the intensity of systemic adverse reactions in Group 1, several related severe adverse events were reported by one subject each (fatigue, crying, eczema and rash pruritic related to ProQuad and Infanrix hexa, otitis media related to Infanrix hexa, bronchitis and rash morbilliform related to ProQuad).

In Group 2, several severe adverse events related to ProQuad were reported by one subject each (irritability, decreased appetite, crying, rash morbilliform and rash vesicular).

In Group 3, only one subject reported a severe systemic event related to Infanrix hexa (diarrhoea).

Assessor's comment:

All systemic reactions listed in the table above are considered to be related to either ProQuad or Infanrix hexa or to no vaccine. For systemic reactions it seems hard to decide, which systemic reaction is caused by which vaccine in group 1.

Temperature

Within 28 days after vaccination 69.3%, 61.1%, and 57.3% of subjects reported body temperature (rectal or equivalent) $\geq 38^{\circ}\text{C}$ (100.4°F) in Groups 1, 2 and 3, respectively. The corresponding number of subjects reporting body temperature $\geq 39.4^{\circ}\text{C}$ were 22.6%, 20.5% and 15.9%.

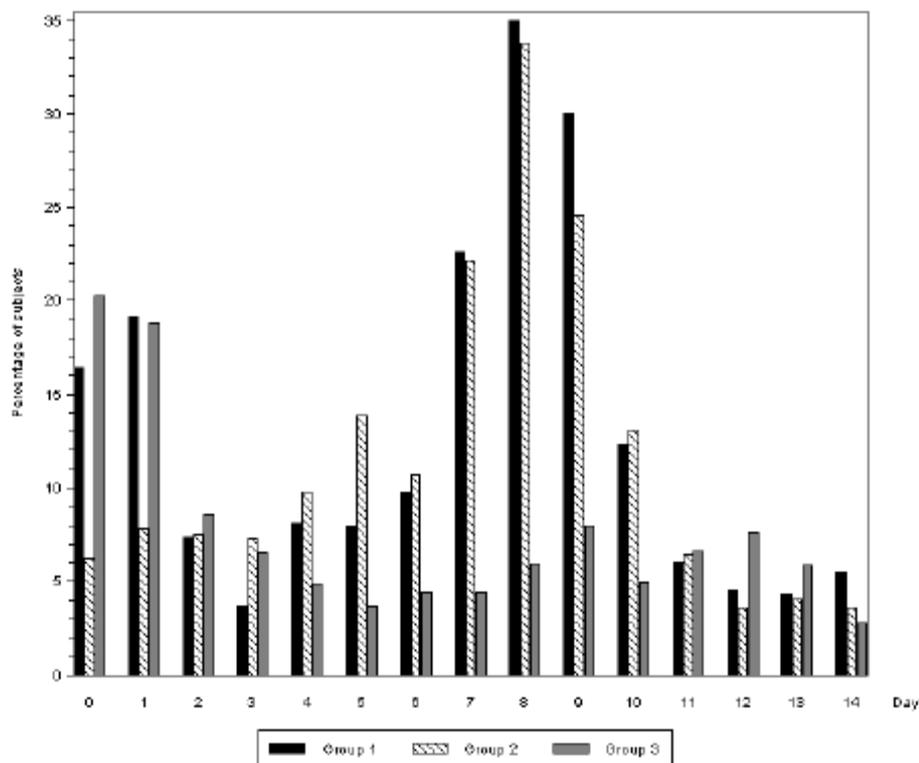
Table 19. Maximal Temperature from Day 0 to Day 28

	Group 1 ProQuad® + Infanrix® hexa (N=474)	Group 2 ProQuad® (N=234)	Group 3 Infanrix® hexa (N=239)
Maximal temperature (rectal or equivalent) [Day 0 – Day 28]			
N	473	234	239
<38°C or normal	145 (30.7%)	91 (38.9%)	102 (42.7%)
$\geq 38^{\circ}\text{C}$	328 (69.3%)	143 (61.1%)	137 (57.3%)
<39.4°C or normal	366 (77.4%)	186 (79.5%)	201 (84.1%)
$\geq 39.4^{\circ}\text{C}$	107 (22.6%)	48 (20.5%)	38 (15.9%)

In Groups 1 and 3, there was an increased number of subjects reporting a body temperature $\geq 38^{\circ}\text{C}$ on Day 0 and Day 1, related to the inactivated vaccine Infanrix hexa and in Groups 1 and 2, there was an increased number of subjects reporting a body temperature $\geq 38^{\circ}\text{C}$ on Days 5 to 10, related to the live vaccine ProQuad., which is shown in the figure 1.

Regarding intensity of pyrexia $\geq 40.0^{\circ}\text{C}$ related to ProQuad were reported by 7 (1.5%) subjects in Group 1 and 4 (1.7%) in Group 2. Pyrexia $\geq 40.0^{\circ}\text{C}$ related to Infanrix hexa were reported by 3 subjects (0.6%) in Group 1 and 2 subjects (0.8%) in Group 3.

Figure 1 Subjects Experiencing a Rectal (or Equivalent) Temperature $\geq 38^{\circ}\text{C}$ between Day 0 and Day 14 Following Vaccination with ProQuad and/or Infanrix hexa



Assessor's Comment:

Overall the percentage of systemic reactions, which were observed, is comparable in all three groups. Within the CSR concomitant medications were not listed, which could have an influence on the fever-rates and/or intensity of temperature.

Injection-site Rashes

From Day 0 to Day 28, 14 (3.0%) and 10 (4.3%) subjects reported injection-site rashes of interest in Groups 1 and 2, respectively and 2 (0.8%) subjects in Group3 (Table 20) None of injection-site rashes was a zoster-like rash. All injection-site rashes were of mild or moderate intensity, most of them (9 in Group 1 and 6 in Group 2) started between Day 5 and Day 12, and most lasted between 1 and 7 days. One rash in Group 1 lasted more than 14 days and 1 in Group 2 was still ongoing at the end of the study.

There were no reports of mumps disease/mumps-like illness in any group during the study.

Table 20. Injection site rashes

	Group 1 (N=474)	Group 2 (N=234)	Group 3 (N=239)
Nb of subjects with at least one Injection-site rash	14 (3.0%)	10 (4.3%)	2 (0.8%)
Number of Injection-site rash			
n	14	10	2
Varicella-like rash	3	2	0
Measles-like rash	7	7	0
Rubella-like rash	4	1	2
Zoster-like rash	0	0	0
Investigator opinion, disease?			
n	0	0	0
Varicella	0	0	0
Measles	0	0	0
Rubella	0	0	0
Zoster	0	0	0
AE intensity			
n	13	9	1
Mild	10	9	1
Moderate	3	0	0
Missing	1	1	1
Specific type of lesions reported (*)			

Non-Injection site rashes

From Day 0 to Day 28, no measles diseases were reported. A comparable proportion of subjects reported measles-like rashes in Group 1 (ProQuad + Infanrix hexa) (33 subjects (7.0%) experienced 36 rashes including 2 rashes of severe intensity), and Group 2 (ProQuad alone) (16 subjects (6.8%) experienced 16 rashes including 1 rash of severe intensity). Most rashes started between Day 5 and Day 12 in both Group 1 (22 rashes) and Group 2 (10 rashes), and in both groups most lasted between 1 and 7 days. In both groups, 1 rash lasted more than 14 days.

During the same safety collection period [Day 0-Day 28], 5 subjects (2.1%) from Group 3, who did not received a ProQuad vaccination, reported 6 measles-like rashes of which 1 was of severe intensity. Most rashes (4) started between Day 0 and Day 4 and all lasted 1-7 days.

From Day 0 to Day 28, no rubellas were reported. Rubella-like rashes were reported by 18 subjects (3.8%) in Group 1 (18 rashes), and 6 subjects (2.6%) in Group 2 (6 rashes), all rashes being of mild or moderate intensity. Most rashes started between Day 5 and Day 12 in Group 1, and between Day 0 and Day 4 in Group 2, and in both groups most lasted 1 to 7 days. The duration was greater than 14 days for 3 rashes in Group 1 and it was 8 to 14 days for 2 rashes in Group 2.

During the same safety collection period [Day 0-Day 28], 1 subject from Group 3, who did not received a ProQuad vaccination, reported 1 rubella-like rash of mild intensity which started between Day 0 and Day 4 and lasted 1 to 3 days.

From Day 0 to Day 28, 1 zoster-like rash (0.2%) was reported in Group 1 (zoster-like rash of mild intensity, with papular lesions, which started during the first 4 days and lasted 2 days), and 1 (0.4%) was reported in Group 2 (zoster-like rash of severe intensity, with vesicular lesions, which started between Day 5 and Day 12 and lasted more than 14 days). No non-injection site zoster/zoster-like rash was reported in Group 3 (Infanrix hexa alone).

From Day 0 to Day 28, varicella/varicella-like rashes were reported by 15 subjects (3.2%) in Group 1 (14 non-injection varicella-like rashes and 2 varicella diseases), 2 subjects (0.9%) in Group 2 (2 non-injection varicella-like rashes), and 3 subjects (1.3%) in Group 3 (3 non-injection varicella-like rashes). In Group 1 most of the rashes started between Day 5 and Day 12, in Group 2, 1 rash started between Day 5 and Day 12 and 1 between Day 13 and Day 21, and in Group 3 rashes started between Day 0 and Day 4. All rashes were of mild or moderate intensity, and most lasted between 1 and 7 days. Respectively 3, 1 and 1 rashes lasted more than 14 days in Group 1, Group 2 and Group 3.

Neither mumps nor mumps-like illness was reported in this study.

Table 21. Non-injection site rashes

Rashes		Group 1 (N=474)	Group 2 (N=234)	Group 3 (N=239)
<i>Measles</i>	Number of subjects with at least one systemic Measles/non-injection site Measles-like rash	33 (7.0%)	16 (6.8%)	5 (2.1%)
AE intensity	n	36	16	6
	Mild	21	10	3
	Moderate	13	5	2
	Severe	2	1	1
<i>Rubella</i>	Number of subjects with at least one systemic Rubella/non-injection site Rubella-like rash	18 (3.8%)	6 (2.6%)	1 (0.4)
AE intensity	n	17	6	1
	Mild	14	4	1
	Moderate	4	2	0
	Missing	1	0	0
<i>Zoster</i>	Number of subjects with at least one systemic Zoster/non-injection site Zoster-like rash	1 (0.2%)	1 (0.4%)	0 (0.0%)
	Zoster-like rash	1	1	0
AE intensity	n	1	1	0
	Mild	1	0	0
	Severe	0	1	0
<i>Varicella</i>	Number of subjects with at least one systemic Varicella/non-injection site Varicella-like rash	15 (3.2%)	2 (0.9%)	3 (1.3%)
	Varicella-like rash	14	2	3
	Varicella disease	2	0	0
AE intensity	n	16	2	3

	Mild	10	1	1
	Moderate	6	1	2

Assessor's comment:

Of note, non-injection site rashes occurred in Group 3 (without ProQuad injection) with a low percentage. Measles-like rashes were reported with a frequency of 2.1% and Varicella-like rashes with a frequency of 1.3% although no MMRV-vaccine was administered in Group 3. Most likely these non-injection site rashes indicate natural infection.

A higher percentage of non-injection site varicella like rashes was reported in the concomitant group in comparison to the non-concomitant group ProQuad. Adding the percentage of non-injection site rashes of the non-concomitant groups it was found that the percentage is comparable with the concomitant group.

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

This study was designed to assess the immunogenicity and safety of concomitant administration of ProQuad with Infanrix hexa, when a first dose of ProQuad is administered to subjects from 12 to 23 months of age concomitantly with a booster dose of Infanrix hexa either as a third dose (2+1 schedule) or a fourth dose (3+1 schedule). The immunogenicity results demonstrate that following concomitant administration of ProQuad with Infanrix hexa no clinically relevant interference in the antibody response to each of the individual antigens is observed. Generally higher response rates and antibody titres were obtained, when both vaccines were given concomitantly compared to the administration of each vaccine alone. The immunisation schedule (3+1 vs 2+1) had limited impact on the immunogenicity results and differences observed were previously reported for other concomitant use studies of Infanrix hexa with childhood vaccines.

As to be expected after concomitant administration a higher percentage of adverse reactions were observed than after administration of each vaccine alone. More subjects reported at least one solicited injection-site adverse reaction related to ProQuad in the concomitant group compared to the non-concomitant group, whereas a numerically comparable number of subjects reported systemic adverse events related to ProQuad in both groups.

The frequency of adverse reactions in the concomitant group is comparable that of the combined frequency of adverse reactions found after administration of both vaccines alone. Only non-injection site varicella-like rashes were reported more frequently in the concomitant group compared to the ProQuad alone. The safety profile following concomitant administration is comparable in terms of incidence and nature of adverse events to that following separate administration of the vaccines. All observed adverse events are already known and described in the SmPCs.

No list of concomitant medication is available in the CSR, therefore the MAH is asked to provide this information.

In conclusion the immunogenicity and safety data of study X06-MMRV-302 support the concomitant administration of ProQuad with Infanrix hexa.

The MAH is asked to update the SmPC to include information on concomitant administration of ProQuad with Infanrix hexa.

PAC No. P046 038

Overall Conclusion:

PAC fulfilled (all commitments fulfilled) - No further action required

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

The MAH is asked to provide further information on concomitant medication given during the conduct of study X06-MMRV-302.

As outcome of this assessment, the MAH is requested to update the Product Information as follows ~~and to submit the corresponding variation by <due date>~~:

Add information on concomitant administration of ProQuad with Infanrix hexa