16 October 2014
EMA/640073/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report under Article 46

ProQuad

measles, mumps, rubella and varicella vaccine, live

Procedure No. EMA/H/C/000622/P46/041

Note

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

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1. ASSESSMENT

Introduction

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

In accordance with Article 46 of Regulation (EC) No 1901/2006 the MAH provides the final clinical study report for the study 'An open-label, multicentre study of the safety of a 2-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad) manufactured with recombinant human albumin (rHA) when administered to children in their second year of life, MRV01C.

Assessment

Rationale for the study

In order to fulfill a post authorization commitment related to the marketing authorisation of M-M-RVAXPRO (EMEA/H/C/604), the MAH proposed to provide additional safety data for its measles, mumps and rubella vaccine manufactured with recombinant human albumin (rHA) instead of human serum albumin (HSA). The MAH proposed to fulfill this commitment by conducting a phase III clinical safety study with ProQuad manufactured with rHA. This proposal was accepted by the CHMP in November 2006.

ProQuad is currently manufactured using pooled serum-derived HSA. However, based on the same rationale as for M-M-RVAXPRO, the substitution of HSA by rHA in the bulk manufacturing process of ProQuad is under development. rHA is structurally and analytically comparable to the unmodified monomeric population of HSA. Thus, rHA and HSA, which are essentially similar, are considered functionally comparable for the production of viral bulks. Experimental data have confirmed that the substitution of HSA by rHA in the viral growth media results in satisfactory vaccine virus growth and product characteristics. However, concerns were raised whether repeated administration of MMR vaccines containing traces of rHA might lead to a higher rate of hypersensitivity/allergic reactions.

The primary objective of study MRV01C was to provide additional safety data in relationship to the new vaccine manufacturing process using rHA. The specific study design was reviewed and approved by CHMP in May 2007.

Study design

Study MRV01C was an open-label study evaluating 2 doses of ProQuad/rHA administered 4 weeks apart in 3340 children 12 to 22 months of age. No control group was included. The safety follow-up period after each dose was planned to be 28 days to 42 days, which was a total of 56 to 84 days of safety follow-up. The study has been conducted in Denmark, Germany, Greece, Italy, Netherlands, Spain and Sweden from October 2007 (FVFS) to November 2008 (LVLS).

The main inclusion criteria were as follows:

Healthy infants aged 12 to 22 months; consent form signed by parent(s) or legal representative; no vaccination history and/or suspected clinical history and/or exposure in the past 30 days to measles, mumps, rubella, varicella and/or zoster; no history of febrile illness (defined as rectal temperature >=38.0°C) in the past 3 days; no known personal history of encephalopathy, seizure disorder or

progressive, evolving or unstable neurological condition; no known sensitivity and/or allergy to any component of the study vaccine; no impairment of the immune system (including receipt of systemic corticosteroids for more than 14 days); no receipt of inactivated vaccine in the past 14 days or live vaccine in the past 28 days.

The inclusion/non-inclusion criteria were in accordance with the approved SmPC of ProQuad.

Objectives and Endpoints:

Primary objective:

To describe the safety profile of a second dose of ProQuad manufactured with rHA when administered to children in their second year of life

Secondary objective:

To describe the safety profile of a first dose of ProQuad manufactured with rHA when administered to children in their second year of life

Primary endpoint:

The primary safety objective of this study will describe the safety profile of a second dose of ProQuad manufactured with rHA when administered to children in their second year of life.

No formal statistical hypothesis has been tested

Secondary endpoint:

The secondary safety objective of this study will describe the safety profile of a first dose of ProQuad manufactured with rHA when administered to children in their second year of life.

These analyses will describe injection-site adverse reactions, systemic adverse events, daily temperatures, rashes and mumps-like illness and serious adverse events.

Safety evaluations:

For both evaluations, i.e. after the second dose of ProQuad (primary objective) and after the first dose of ProQuad (secondary objective), the safety criteria were as follows:

- From Day 0 to Day 4 following each dose solicited injection-site adverse reactions (i.e. injection-site erythema, injection-site swelling, injection-site pain) were evaluated:
- From Day 0 to Day 28 following each dose the following evaluations were conducted
    - Unsolicited injection-site adverse reactions,
    - Numeric values of temperature,
    - Systemic adverse events:
        - Measles-like rash
        - Mumps-like illness
        - Rubella-like rash
        - Varicella-like rash
        - Zoster-like rash
    - Other systemic adverse events

- From Day 0 to the next visit (or last visit in case of premature discontinuation) all serious adverse events were evaluated.

No formal statistical hypothesis was tested. Injection-site adverse reactions, systemic adverse events, numerical values of temperature, rashes, mumps-like illnesses and serious adverse events were described.

Results

Demographic characteristics:

At the date of first vaccination, the mean age of the 3,388 vaccinated subjects was 14.6 months (range 11.5 – 23.8). There were 1,650 (48.7%) girls and 1,738 (51.3%) boys. Their mean weight was 10.4 kg (range 7 – 17) and their mean height was 78.3 cm (range 67 – 97).

Most subjects (3,367 out of 3,388, 99.38%) received a previous vaccination: Mainly combined bacterial and viral vaccines (e.g. Pentavac, INFANRIX hexa, INFANRIX-IPV+Hib) for 3348 subjects (98.82%) and pneumococcal vaccines, for 2783 subjects (82.14%).

Two subjects (0.06%), subjects 58041 and 67014, were included although they had already received a first dose of MMR vaccine (Triple Virica). This finding, which constituted a protocol deviation, was not known at baseline. These two subjects were withdrawn after the first injection of ProQuad thus the recommended schedule of 2 doses of MMR vaccine was followed for the concerned subjects.

Out of 3388 subjects included, 12 did not present follow-up data after the first administration and were not included in the post-dose 1 safety set and 34 subjects did not present follow-up data after the second dose.

Protocol Deviations:

A total of 487 subjects out of 3388 vaccinated subjects, i.e. 14.37%, presented at least one protocol deviation. The most frequent type of deviation was related to a poor compliance with the immunization schedule (246 subjects; 7.26%), and with the time intervals between visits (344 subjects; 10.15%). Seven subjects (0.21%) received non-study vaccine(s), between Visit 2 and Visit 3, which constituted protocol deviations.

Concomitant medications:

A total of 1127 subjects (33.26%) received at least one concomitant medication for prophylaxis or adverse events following the first dose; a majority of the treatments were anilides (991 subjects, 29.25%). A total of 601 subjects (17.74%) received at least one treatment following the second dose; a majority of the treatments were anilides (503 subjects, 14.85%).

Safety evaluation

Post dose 2

From Day 0 to Day 28 after the second dose, 57.66% of subjects reported at least one adverse event, 34.23% reported at least one injection-site adverse reaction and 40.42% reported at least one systemic adverse event (Table 1).

Table 1: Global summary of safety following the second dose of ProQuad (Safety Set Post-Dose 2)

	Second dose (N=3342)	
	n (%)	[IC 95%]
Adverse events from Day 0 to Day 28	1927 (57.66)	[55.96; 59.34]
Vaccine-related adverse event from Day 0 to Day 28	1396 (41.77)	[40.09; 43.47]
Injection-site adverse reaction from Day 0 to Day 28	1144 (34.23)	[32.62; 35.87]
Solicited injection-site reaction from Day 0 to Day 4	1127 (33.72)	[32.12; 35.35]
Injection site erythema	1018 (30.46)	[28.90; 32.05]
Injection site swelling	442 (13.23)	[12.09; 14.42]
Injection site pain	384 (11.49)	[10.43; 12.62]
Unsolicited injection-site adverse reaction from Day 0 to Day 28	55 (1.65)	[1.24; 2.14]
Systemic adverse event from Day 0 to Day 28	1351 (40.42)	[38.76; 42.11]
Vaccine-related systemic adverse event from Day 0 to Day 28	449 (13.44)	[12.30; 14.64]
Injection-site rash of interest from Day 0 to Day 28	1 (a) (0.03)	[0.00; 0.17]
Non-injection-site rash of interest from Day 0 to Day 28	93 (2.78)	[2.25; 3.40]
Measles / Measles-like rash	54 (1.62)	[1.22; 2.10]
Rubella / Rubella-like rash	19 (0.57)	[0.34; 0.89]
Varicella / Varicella-like rash	21 (0.63)	[0.39; 0.96]
Zoster / Zoster-like rash	1 (0.03)	[0.00; 0.17]
Mumps / Mumps-like illness from Day 0 to Day 28	1 (b) (0.03)	[0.00; 0.17]
Serious adverse event from Visit 2 to Visit 3	22 (0.66)	[0.41; 0.99]
Vaccine-related serious adverse event from Visit 2 to Visit 3	7 (0.21)	[0.08; 0.43]
Withdrawal for adverse event from Visit 2 to Visit 3	0 (0)	[0.00; 0.11]
Withdrawal for vaccine-related adverse event from Visit 2 to Visit 3	0 (0)	[0.00; 0.11]
Withdrawal for vaccine-related serious adverse event from Visit 2 to Visit 3	0 (0)	[0.00; 0.11]
Withdrawal for vaccine-related non-serious adverse event from Visit 2 to Visit 3	0 (0)	[0.00; 0.11]

(a) one case of varicella-like rash
(b) one case of mumps-like illness

Regarding injection-site adverse reactions, between Day 0 and Day 4, 33.72% subjects reported at least one solicited injection-site reaction (erythema: 30.46%, swelling: 13.23% and pain: 11.49%). One subject reported an injection-site rash of interest (varicella-like rash).

A total of 13.44% of subjects reported at least one vaccine-related systemic adverse event within 28 days after the second dose. The most frequently reported vaccine-related systemic adverse events (reported by more than 1% of subjects) were pyrexia (7.93%) and rash morbilliform (1.50%).

A total of 16 (0.48%) subjects reported allergic-type adverse events (Preferred Terms - PTs: urticaria, dermatitis allergic, drug hypersensitivity, bronchospasm, pruritus). No anaphylactic reactions were reported. All these events were non-serious adverse events and 5 of them were vaccine-related according to the investigator: urticarial (2 subjects); drug hypersensitivity (1 subject); dermatitis allergic (1 subject) and pruritus (1 subject).

A total of 93 (2.78%) subjects reported non injection-site rashes of interest: measles-like rash: 1.62% (PT: rash morbilliform: 54 subjects), rubella-like rash: 0.57% (PT: rash rubelliform: 19 subjects), varicella-like rash: 0.63% (PT: rash vesicular: 21 subjects) and zoster-like rash: 0.03% (PT: rash vesicular: 1 subject).

Regarding body temperature, 26.12% of subjects reported rectal (or equivalent) temperature ≥38.0°C and 12.06% of subjects reported rectal temperature ≥39.4°C.

A total of 22 (0.7%) subjects reported a total of 25 serious adverse events following the second dose, including 7 vaccine-related serious adverse events: febrile convulsion (4 subjects), cyanosis (assessed

as Suspected Unexpected Serious Adverse Reaction, possible related – SUSAR: 1 subject), pyrexia (1 subject), bronchitis (1 subject).

No adverse event leading to withdrawal was reported after the second dose.

In addition to adverse events following the second dose of ProQuad as presented above (see Table 1) 26.12% of subjects reported rectal temperature (or equivalent) ≥38.0°C and 12.06% of subjects reported rectal temperature ≥39.4°C. Twelve subjects (0.36%) presented rectal (or equivalent) temperature at or higher than 41°C (max. 41.5°C).

A total of 204 subjects (6.10%) presented at least one systemic adverse event of severe intensity; among these subjects, 53 subjects (1.59%) presented vaccine-related systemic adverse events of severe intensity. The most frequent severe vaccine-related were pyrexia (38 subjects; 1.14%), rash (3 subjects, 0.09%) and severe rash morbilliform (4 subjects, 0.12%) and ear infection (2 subjects, 0.06%).

All other vaccine-related systemic adverse events of severe intensity were of single occurrence (0.03%). They include 2 allergic-type reactions (drug hypersensitivity and urticarial) and one febrile convulsion.

Post dose 1 (secondary objective)

From Day 0 to Day 28 after the first dose, 71.62% of subjects reported at least one adverse event, 26.27% reported at least one injection-site adverse reaction and 64.10% reported at least one systemic adverse event (Table 2).

Table 2: Global summary of safety following the first dose of ProQuad (Safety Set Post-Dose 1)

	First dose (N=3376)	
	n (%)	[IC 95%]
Adverse events from Day 0 to Day 28	2418 (71.62)	[70.07; 73.14]
Vaccine-related adverse event from Day 0 to Day 28	1709 (50.62)	[48.92; 52.32]
Injection-site adverse reaction from Day 0 to Day 28	887 (26.27)	[24.80; 27.79]
Solicited injection-site reaction from Day 0 to Day 4	723 (21.42)	[20.04; 22.84]
Injection site erythema	483 (14.31)	[13.14; 15.53]
Injection site swelling	188 (5.57)	[4.82; 6.40]
Injection site pain	348 (10.31)	[9.30; 11.38]
Unsolicited injection-site adverse reaction from Day 0 to Day 28	251 (7.43)	[6.57; 8.37]
Systemic adverse event from Day 0 to Day 28	2164 (64.10)	[62.45; 65.72]
Vaccine-related systemic adverse event from Day 0 to Day 28	1177 (34.86)	[33.26; 36.50]
Injection-site rash of interest from Day 0 to Day 28	16 (a) (0.47)	[0.27; 0.77]
Non-injection-site rash of interest from Day 0 to Day 28	385 (11.40)	[10.35; 12.52]
Measles / Measles-like rash	233 (6.90)	[6.07; 7.81]
Rubella / Rubella-like rash	98 (2.90)	[2.36; 3.53]
Varicella / Varicella-like rash	71 (2.10)	[1.65; 2.65]
Zoster / Zoster-like rash	1 (0.03)	[0.00; 0.16]
Mumps / Mumps-like illness from Day 0 to Day 28	7 (b) (0.21)	[0.08; 0.43]
Serious adverse event from Visit 1 to Visit 2	40 (1.18)	[0.85; 1.61]
Vaccine-related serious adverse event from Visit 1 to Visit 2	15 (0.44)	[0.25; 0.73]
Withdrawal for adverse event from Visit 1 to Visit 2	8 (0.24)	[0.10; 0.47]
Withdrawal for vaccine-related adverse event from Visit 1 to Visit 2	6 (0.18)	[0.07; 0.39]
Withdrawal for vaccine-related serious adverse event from Visit 1 to Visit 2	3 (0.09)	[0.02; 0.26]
Withdrawal for vaccine-related non-serious adverse event from Visit 1 to Visit 2	3 (0.09)	[0.02; 0.26]

(a) 16 cases: measles-like rash (3 subjects), rubella-like rash (2 subjects) and varicella-like rash (11 subjects)
(b) 7 cases of mumps-like illness

Regarding injection-site adverse reactions, between Day 0 and Day 4, 21.42% subjects reported at least one solicited injection-site reaction (erythema: 14.31%, swelling: 5.57% and pain: 10.31%). A total of 16 subjects (0.47%) reported an injection-site rash of interest (measles-like rash: 3 subjects, rubella-like rash: 2 subjects and varicella-like rash: 11 subjects).

A total of 34.86% of subjects reported at least one vaccine-related systemic adverse event within 28 days after the first dose. The most frequently reported vaccine-related systemic adverse events (reported by more than 1% of subjects) were pyrexia (21.45%), rash morbilliform (6.58%), rash (2.49%), rash rubelliform (2.31%), rash vesicular (1.81%), diarrhoea (1.18%) and nasopharyngitis (1.07%).

A total of 21 (0.62%) subjects reported allergic-type adverse events (PTs: urticaria, dermatitis allergic, drug hypersensitivity, bronchospasm, pruritus, swelling face). No anaphylactic reactions were reported. All these events were non-serious adverse events and 5 of them were vaccine-related according to the investigator: urticarial (2 subjects), dermatitis allergic (2 subjects) and pruritus (1 subject).

A total of 385 (11.40%) subjects reported non-injection-site *rashes of interest*: measles/measles-like rash: 6.90% (PT: measles: 1 subject; PT: rash morbilliform: 232 subjects), rubella/rubella-like rash: 2.90% (PT: rubella: 2 subjects; PT: rash rubelliform: 96 subjects), varicella/varicella-like rash: 2.10%

(PT: varicella: 5 subjects; PT: rash vesicular: 66 subjects) and zoster-like rash: 0.03% (PT: rash vesicular: 1 subject).

A total of 40 (1.2%) subjects reported a total of 45 serious adverse events following the first dose, including 17 vaccine-related serious adverse events reported by 15 subjects: febrile convulsion (8 subjects), pneumonia (assessed as SUSAR, possible related: 1 subject reported 2 episodes), loss of consciousness (assessed as SUSAR possible related, 1 subject), pyrexia (at 39.2°C, associated with non-vaccine-related serious upper respiratory tract infection and vaccine-related febrile convulsion) (1 subject), acute tonsillitis (1 subject), gastroenteritis (1 subject), viral infection (1 subject), asthma (1 subject), rash (1 subject).

Eight (0.2%) subjects were withdrawn from the study due to an adverse event occurring after the first dose: 2 of these adverse events were assessed by the investigator as unrelated to vaccine (varicella and vomiting), and among the 6 assessed as vaccine-related, 3 were non-serious (dermatitis allergic, rash rubelliform, and erythema multiforme minor), and 3 were serious (pneumonia: SUSAR, febrile convulsion, and asthma).

In addition to adverse events following the first dose of ProQuad (Table 2) 56.10% of subjects reported rectal temperature ≥38.0°C and 25.24% of subjects reported rectal temperature ≥39.4°C. Twenty-one subjects (0.62%) presented a rectal (or equivalent) temperature at or higher than 41°C (max. 42.1°C).

Adverse events of severe intensity:

A total of 330 subjects (9.77%) presented at least one systemic adverse event of severe intensity; among these subjects, 151 subjects (4.47%) presented vaccine-related systemic adverse events of severe intensity. The most frequent vaccine-related systemic adverse events of severe intensity were:

- pyrexia: 112 subjects (3.32%)
- nasopharyngitis: 5 subjects (0.15%),
- rash rubelliform: 4 subjects (0.12%),
- diarrhoea: 3 subjects (0.09%),
- ear infection: 3 subjects (0.09%),
- gastroenteritis: 3 subjects (0.09%),
- febrile convulsion: 3 subjects (0.09%),
- rash: 3 subjects (0.09%),
- rash morbilliform: 3 subjects (0.09%),
- insomnia: 2 subjects (0.06%),
- vomiting: 2 subjects (0.06%)

No deaths were reported during the course of the study.

2. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

The primary objective of study MRV01C was to provide additional safety data in relationship to the new vaccine manufacturing process using rHA. Specifically the MAH was asked to investigate the occurrence of adverse events related to hypersensitivity/allergic reactions following repeated doses of rHA containing vaccines. The rates of adverse reactions after the second dose of ProQuad were generally similar to, or lower than, those seen after the first dose. Especially the rate of allergic-type adverse events did not increase after the second dose. Only the injection side adverse events,

particularly the rate of erythema, were lower post dose 1 compared with post dose 2. However, most of these events were mild.

Overall, the safety profile of ProQuad manufactured with rHA is in accordance with the currently approved SmPC of ProQuad manufactured with HSA indicating that there is no increased risk of allergic reactions or other adverse events due to the use of rHA instead of HSA.

However, it should be noted that after the second dose of ProQuad the solicited injection-site adverse reactions from Day 0 to Day 4 increase from 21.42% after the first dose, to 33.72% after the second dose. In particular, the injection site erythema is reported by 14.31% of individuals after the first dose and by 30.46% of individuals after the second dose; injection site swelling increases from 5.57% after the first dose to 13.23% after the second dose. Notwithstanding, considering that the increase is mainly due to events of mild or moderate intensity, it can be concluded that the safety profile of ProQuad manufactured with rHA is in accordance with the currently approved SmPC of ProQuad manufactured with HSA.

However, the MAH should present a type II variation to update section 4.8 of the SmPC in order to reflect the observed increase in the injection-site adverse reactions following the second dose of ProQuad. The wording “The rates of adverse reactions after the second dose of ProQuad were generally similar to, or lower than, those seen with the first dose” is no longer acceptable.

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

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

The MAH is required to submit by 01.03.2011 the following variation(s):

Update of section 4.8 to amend information on increase in injection site adverse reactions.

Moreover, the MAH is asked to include a warning statement for patients with rare hereditary problems of fructose intolerance, since sorbitol is present in the vaccine. This is in accordance with the guideline on excipients and was unfortunately deleted during previous procedures.