26 June 2014
EMA/655900/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under article 46

ProQuad

Measles, mumps, rubella and varicella vaccine, live

Procedure no: EMEA/H/C/00622/P046/0053

Note

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

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Table of Contents

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 'A Multicenter, Randomized, Open-Label Study to Compare the Immunogenicity, Safety, and Tolerability of Measles, Mumps, Rubella, and Varicella of Combination Vaccine ProQuad with Concomitant Administration of M-M-R II and VARIVAX in Healthy Korean Children'.

Assessment

Rationale for the study

The study was planned to support registration of ProQuad in South Korea (Protocol 023).

Study design

Study P023 was an open-label study evaluating the immunogenicity, safety, and tolerability of a single dose of ProQuad in comparison with concomitant vaccination of M-M-R II and VARIVAX in healthy children. Blood samples were to be obtained just prior to vaccination (Day 1) and at 6 weeks (between Days 35 and 56) after vaccination. The safety follow-up period after each dose was planned to be 28 days following vaccination using. The study has been conducted in Korea in 2008.

The intended study population was healthy children, 12 months to 23 months of age, who had a negative clinical history for measles, mumps, rubella, varicella, and herpes zoster. Exclusion criteria included previous vaccination with measles, mumps, rubella, and/or varicella vaccines (either alone or in any combination), and congenital or acquired immune deficiency.

Approximately 360 subjects were planned to be randomized in a 1:1 ratio to receive either ProQuad on Day 1, or M-M-R II and VARIVAX concomitantly on Day 1. After 30 subjects were enrolled into this study, enrollment was suspended in April 2008 when a U.S. Advisory Committee on Immunization Practices (ACIP) Working Group from the Centers for Disease Control and Prevention (CDC) was established to evaluate the risk of febrile seizures following vaccination with ProQuad. In October 2009, the ACIP updated their recommendations that for the first dose of measles, mumps, rubella, and varicella vaccines at ages 12 through 47 months, either separate MMR and varicella vaccines or MMRV vaccine can be used. At that time, it was not possible to complete enrollment into Protocol 023 before the expiry date of the investigational vaccine lot. For this reason, the study was terminated early, and only 30 subjects were enrolled.

The primary objective of study P023 was to demonstrate that the MAHs measles, mumps, rubella, and varicella vaccine ProQuad induces antibody response rates that are non-inferior to concomitant administration of the combined measles, mumps and rubella vaccine M-M-R II and the monovalent varicella vaccine VARIVAX. Secondary objective was demonstration of non-inferiority as regards GMT.

Primary immunogenicity analyses were performed for the antibody response rates and GMTs at 6 weeks postvaccination in the group receiving ProQuad and the group receiving M-M-R II and VARIVAX. The population for the primary immunogenicity analysis was the PPS.

Given the limited enrollment, it was not able to formally test the original hypotheses in this study.

Response rates (RR) six weeks after the administration of the study vaccines were summarized and the 90% confidence interval (CI) of the difference in proportion was provided. With respect to measles, mumps, rubella, and varicella the GMTs six weeks postvaccination of the study vaccines were summarized, and the 90% CI of the ratio of GMTs was provided.

The primary safety variables included vaccine-related SAEs, fever, measles-, rubella-, varicella, zoster-like rashes and mumps-like symptoms as well as injection site AEs.

Safety was evaluated for 28 days following vaccination using a Vaccination Report Card (VRC), which had to be completed by the parent/guardian. The VRC was reviewed during the final visit on approximately Day 42 by study personnel. The parent/guardian was instructed to contact study personnel if the subject developed a measles-like rash, a rubella-like rash, a varicella-like rash, a zoster-like rash, or symptoms compatible with mumps.

Results

Study population

In total 30 out of the 360 children planned to be enrolled were actually randomized to one of the two vaccination groups (ProQuad: 13 children; MMR II/Varivax: 17 children). All children were 12 to 17 months of age. A total of 28 subjects completed the study. One subject was excluded due to receipt of another vaccine within 30 days prior to study start and another subject was lost to follow-up following vaccination.

Immunogenicity

The immunogenicity analysis from the recruited subjects indicated that the 6-week postvaccination response rates and GMTs for measles, mumps, rubella, and varicella in the two vaccination groups are comparable and reflect the outcome from previous clinical trials.

Safety evaluation

The safety profile was comparable between both vaccination groups according to the reported frequency of rashes and fever, which was the objective of the trial. The occurrence of injection site AEs was reported by 3 subjects in the ProQuad group and none in the MMR II/Varivax group.

Two non-serious-adverse experiences during the 6-week postvaccination period were reported: one of diaper dermatitis and one of skin and subcutaneous tissue disorder. Both were observed in the ProQuad group.

One subject of the MMR II/Varivax group reported two SAEs, because the boy was hospitalized and treated for fever and systemic measles-like rash. Onset of fever was at day 10 after vaccination and lasted 4 days with moderate intensity, while the rash started on day 11 and was resolved after 7 days. Intensity of the rash was not reported.

Overall, the analysis from the small number of recruited children showed a similar safety profile in both vaccination groups, which was observed in correlated trials for the approval of ProQuad.

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

Study P023 revealed no relevant information regarding the immunogenicity or safety profiles that are not reflected in the currently approved product information of ProQuad. Hence, no amendment to the approved product information is required.

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

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