



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Gardasil 9

human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

Procedure no: EMEA/H/C/003852/P46/002

Note

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



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1. Introduction

In June, 2016, the MAH submitted a completed paediatric extension study for Gardasil 9, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Gardasil 9 and therefore no amendments to the product information have been identified.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The 9-valent human papillomavirus (9vHPV) (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) recombinant vaccine [GARDASIL™9], also referred to as the 9vHPV vaccine, is an aluminum-adsorbed recombinant protein particulate virus-like particle (VLP) vaccine manufactured by Merck & Co., Inc. (Whitehouse Station, New Jersey, USA).

The 9vHPV vaccine was developed to provide protection against infection and disease caused by 7 cancer-causing HPV types (HPV 16, 18, 31, 33, 45, 52 and 58), which are together responsible for approximately 90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers worldwide, and 2 HPV types (HPV 6 and 11) which are responsible for 90% of genital warts [Ref. 5.4: 03RSDR, 03RTW5, 0409ZR, 040GSK, 03RJDL]. In a Phase 3 clinical study, the 9vHPV vaccine prevented infection and disease due to the HPV vaccine types in females 16 to 26 years of age. The 9vHPV vaccine was licensed in the United States in 2014; in Canada, the European Union, and Australia in 2015; and in other countries in 2015/2016 under the trade name GARDASIL™9.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

V503-006-02, an open-label extension of the V503-006 base study. The results of the V503-006 base study were summarized in a Clinical Study Report included in the original marketing application.

2.3.2. Clinical study

The goal of the extension study V503-006-02 was to offer a 3-dose regimen of 9vHPV vaccine to subjects in the placebo arm of the V503-006 base study. Participation in the study extension was voluntary. Subjects who elected to participate were administered 3 doses of 9vHPV vaccine using a Day 1, Month 2, Month 6 schedule and followed for safety through Month 7. No serum samples were collected.

Description

Methods

The V503-006 base study was designed to include a contingency for an extension phase (V503-006-02) [Ref. 5.3.5.4: 04DDCF]; specifically, the base study protocol stated that subjects randomized to the placebo arm would be eligible to receive 9vHPV vaccine under a study extension following demonstration of vaccine tolerability and immunogenicity. These two conditions were met:

- Based on review of safety from the V503-006 study and the V503 program, in 2011 the external Data Monitoring Committee (eDMC) recommended the vaccination of V503-006 placebo recipients at the completion of the study without reservation [Ref. 5.3.5.4: 04DDCF].
- The pivotal efficacy study of 9vHPV vaccine (V503-001) in young adult women, 16 to 26 years of age demonstrated that the 9vHPV vaccine was immunogenic and prevented infection and disease due to the vaccine HPV types. The V503-001 clinical study report [Ref. 5.3.5.1: P001] was completed on 31-Oct-2013.

The V503-006-02 extension study protocol was released from the Sponsor on 07-Jan-2014. The study was initiated on 08-May-2014. Participation in the study extension was voluntary and subject to a separate informed consent. A total of 306 subjects across 7 countries were enrolled in the placebo arm of the base study and therefore eligible for the extension study. Approval of the V503-006-02 study extension was achieved in 6 countries (including Canada, Colombia, Hong Kong, Mexico, Sweden and the United States), representing 198 subjects who were eligible for the extension study. Because the study extension was not approved in Denmark, the 108 subjects from Denmark enrolled in the placebo arm of the base study were not eligible to participate in the study extension. The study extension was completed on 28-Nov-2015 (last patient last visit). This clinical overview summarizes the results of the V503-006-02 study extension in fulfillment of Article 46.

Immunogenicity/efficacy

Not applicable.

Safety

Subjects who elected to participate in the extension study were administered 3 doses of 9vHPV vaccine at Day 1, Month 2, and Month 6 and followed for safety through Month 7. This included monitoring for serious adverse experiences (SAEs) and pregnancy information. A Vaccination Report Card (VRC) was not used.

Serious adverse events were reportable regardless of causality from the time consent was signed through 1 month following vaccination dose 3. Events of fetal loss were to be reported as SAEs for any pregnancy with a last menstrual period prior to 30 days following final vaccination. Deaths and vaccine-related SAEs were collected for the duration of the extension study.

All subjects underwent pregnancy testing based on urine or serum analyses for β -human chorionic gonadotropin before vaccination. Subjects found to be pregnant were not vaccinated. Females aged 16 years or older at enrollment were instructed to use effective contraception through 30 days following vaccination dose 3. Pregnancies occurring between Day 1 and Month 7 were followed to outcome. Serious AEs for infants born to study participants were collected throughout the study and followed to outcome.

Results

Immunogenicity results

As there were no efficacy or immunogenicity objectives in V503-006-02, this section is not applicable to the current application.

Safety results

Overall Summary of Adverse Events

A total of 102 subjects were enrolled into the V503-006-02 extension. All these subjects received at least one dose of 9vHPV vaccine. Approximately 93% of those enrolled received all three doses of vaccine.

With respect to the adverse events reported during the V503-006-02 extension study, the following observations can be made among the subjects with follow-up data:

- No subjects discontinued study vaccinations due to an adverse event
- No subjects died
- No vaccine-related SAEs were reported
- Two (2) subjects reported SAEs which were not vaccine-related:
 - Abdominal pain that began 7 days post-vaccination and resolved after 2.43 weeks
 - Diarrhea that began 11 days post-vaccination and resolved after 3 days
- Two (2) subjects had pregnancies which resolved without complication

CHMP comment:

No new safety concerns have been identified based on the results from the extension study V503-006-02.

2.3.3. Discussion on clinical aspects

The 9vHPV vaccine was generally well-tolerated in the V503-006-02 study extension. Overall the safety profile in this study extension did not reveal any new findings compared with previous studies in the 9vHPV vaccine clinical program.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The commitment is regarded as fulfilled, through the submission of the full clinical extension study report.

Recommendation

Fulfilled:

No regulatory action required.

Additional clarifications requested

Not applicable.