

Supplementary Appendix

Protocol V501-015: A Registry-based Study in countries with centralized cervical cancer screening infrastructures

This long-term follow-up (LTFU) study in 4 Nordic countries (Denmark, Iceland, Norway, and Sweden) is an ongoing extension of the pivotal phase 3 study that investigated the safety, immunogenicity, and effectiveness of the qHPV vaccine in 16- to 23-year old women.¹ Due to the existence of a unique personal identification number for each citizen and nationwide registries, it is possible to perform studies in this population with virtually no loss to follow-up. All women in the trial are being followed through their respective national registries for vaccine effectiveness as well as immunogenicity and safety, including deaths, cancers, and hospitalizations.

Participation and retention in these countries has been very high with approximately 95% of study participants completing the Month 48 visit of the initial phase 3 study. The study includes 2,700 subjects who originally received the qHPV vaccine and 2,100 subjects who originally received placebo and who were vaccinated with the qHPV vaccine when the initial four-year study was completed. Subjects who originally received placebo and who refused vaccination with qHPV vaccine are also being followed. Effectiveness and safety analyses started ~2 years following completion of this protocol and will be continuously updated every 2 years thereafter for 10 years. In the initial analyses, the qHPV vaccine was well tolerated up to 8 years following vaccination.^{2,3}

Protocol V501-020: Long-term immunogenicity, safety, and effectiveness study in men

This 10-year study provides the first long-term safety data among young males. The long-term safety data analyzed include the incidence of SAEs that a study investigator considered as possibly, probably, or definitely related to prior administration of the qHPV vaccine or to a study procedure and deaths. Of the 2,966 subjects aged 16 to 26 (heterosexual men and men-who-have-sex-with men) who completed the Protocol 020 base study,^{4,5} 1,805 participated in the ongoing LTFU.⁶ Thus far, the median follow-up time post-dose 3 is 5.8 years among those who received the qHPV vaccine in the base study. During the LTFU, two SAEs were reported, but neither was deemed related to vaccine.⁶

Active and Passive Surveillance and Studies in Special Populations (human immunodeficiency virus [HIV]-infected, and those with Systemic Lupus Erythematosus)

Study in HIV-infected young women

HIV-infected women have an increased prevalence of HPV infections and are therefore at higher risk of HPV related disease including cervical cancer. There was concern that HPV vaccines may be less immunogenic in HIV-positive people because of immune compromise in people with HIV. To assess this, the AIDS Clinical Trials Group enrolled 319 HIV-positive girls and women aged 13 to 45 years. The qHPV vaccine was administered on day 1, and weeks 8 and 24, with responses measured 4 weeks after the third dose. Overall, geometric mean titers and seroconversion rates were similar in those with and without HIV. The vaccine was generally safe and well tolerated with only 3 subjects reporting a problem possibly or definitely related to the vaccine (chest pain, back pain, and rash).

Study in HIV-infected children

In an open-label study of the safety and immunogenicity of the qHPV vaccine in 126 HIV-infected children aged 7-12 years, the safety profile of the qHPV vaccine was similar to that previously reported in HIV-uninfected children aged 9-15. AEs were infrequent and their occurrence was similar between HIV-infected qHPV vaccine and placebo recipients. There were, however, more frequent injection site reactions in vaccine recipients which was not statistically significant ($p = 0.19$). The safety profile was similar after each vaccine dose, except for an increase in indirect bilirubin values after the last 2 doses, which was attributed by the study investigators to antiretrovirals. Administration of the qHPV vaccine did not alter the CD4 status or HIV viral load.

Studies in patients with Systemic Lupus Erythematosus (SLE)

In a prospective case-control study of the safety and immunogenicity of the qHPV vaccine in women with SLE, 50 patients with SLE and 50 healthy controls were evaluated. The most common AE was injection site reaction (5%), all of which were mild and subsided spontaneously after 1-2 days. The rate of SLE flares in the SLE subjects was 0.22 per patient per year, and the rate of flares in the matched SLE controls was 0.20 per patient per year, which were not statistically different ($p=0.81$). The authors concluded that the qHPV vaccine is well tolerated in patients with stable SLE.

In a prospective, open-label study of 27 females aged 12 to 26 years, 27, 25 and 20 subjects received one, two and three doses of HPV vaccine, respectively. In this small, non-

randomized, non-controlled prospective study, qHPV vaccine was generally well tolerated and immunogenic in adolescents and young women with SLE.

EudraVigilance

EudraVigilance (<http://eudravigilance.ema.europa.eu/highres.htm>), a central computer database, was created by the EMA in December 2001 to capture AE reports for medicines and vaccines licensed across the European Union (EU).⁷ AE reports are received from the EU regulatory agencies and from pharmaceutical companies and sponsors of clinical trials in the EU. Eudravigilance supports the early detection of possible safety signals associated with medicinal products for human use and the continual monitoring and evaluation of potential safety issues in relation to reported adverse reactions. The data are routinely analysed by regulatory authorities in the EU and companies have access to the information relating to their own medicines. Data from EudraVigilance are published in the European database of suspected adverse drug reaction reports.⁸ This website allows users to view the total number of individual suspected-side-effect reports submitted to EudraVigilance for each centrally authorised medicine. Users can sort these reports by age group, sex, type of suspected side effect and outcome. Reports for common drug substances used in nationally authorised medicines will be published during 2014.

Australian National Surveillance Program

From May 2007 - July 2009, ~1.2 million doses of the qHPV vaccine were distributed in Victoria, Australia. The rate of syncope and seizures reported to SAEFVIC during this period was 7.8 and 2.6 per 100,000 doses distributed, respectively.⁹

Anaphylactic and anaphylactoid reactions have rarely been reported following vaccination with the qHPV vaccine.¹⁰ In 2008, a multidisciplinary team reviewed 12 presumptive cases reported to SAFEVIC. Eight were defined as anaphylaxis (using Brighton case definition) giving an incidence rate of the 2.6 per 100,000 doses, greater than the estimated incidence of 0.1-1 per 100,000 doses of most vaccines.¹⁰ Of note, four of eight reactions classified as anaphylaxis had negative skin testing and intradermal testing with the qHPV vaccine, thereby suggesting that there was no hypersensitivity to vaccination. Studies from other countries, including Canada¹¹ and the US,¹² have reported a rate of anaphylactic and anaphylactoid reactions of ~1 per 1 million recipients of the qHPV vaccine, similar to other vaccines.¹⁰ In 2001 (prior to qHPV vaccine licensure) VAERS recorded 452 reports of anaphylactoid reactions among over 1.9 billion doses of vaccines administered over a 10 year period. For any vaccine, vaccine-associated anaphylaxis is a rare event; nonetheless, providers should be prepared to provide immediate medical treatment should it occur.^{13,14}

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