

Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection

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Objective: In the quadrivalent (types 6/11/16/18) HPV vaccine (GARDASIL®/SILGARD®) clinical program, 73% of women aged 16–26 were naïve to all vaccine HPV types. In these women, prophylactic administration of the vaccine was highly effective in preventing HPV 6/11/16/18-related cervical disease. Of the remaining women, 15% of had evidence of past infection with one or more vaccine HPV types (seropositive and DNA negative) at the time of enrollment. Here we present an analysis in this group of women to determine the efficacy of the HPV 6/11/16/18 vaccine against new cervical and external anogenital disease related to the same vaccine HPV type which had previously been cleared. Vaccine tolerability in this previously infected population was also assessed.

Results: Subjects were followed for an average of 40 months. Seven subjects in the placebo group developed cervical disease, and eight subjects developed external genital disease related to a vaccine HPV type they had previously encountered. No subject receiving HPV 6/11/16/18 vaccine developed disease to a vaccine HPV type to which they were seropositive and DNA negative at enrollment.

Methods: 18,174 women were enrolled into three clinical studies. The data presented comprise a subset of these subjects (n = 2,617) who were HPV seropositive and DNA negative at enrollment (for ≥1 vaccine type). In each study, subjects were randomized in a 1:1 ratio to receive HPV 6/11/16/18 vaccine or placebo at day 1, month 2 and month 6 (without knowledge of baseline HPV status). Procedures performed for efficacy data evaluation included detailed genital examination, Pap testing and collection of cervicovaginal and external genital specimens. Analyses of efficacy were carried out in a population stratified by HPV serology and HPV DNA status at enrollment.

Conclusions: These results suggest that natural HPV infection-elicited antibodies may not provide complete protection over time, however the immune response to the HPV 6/11/16/18 vaccine appears to prevent reinfection or reactivation of disease with vaccine HPV types. Vaccine-related adverse experiences were higher among subjects receiving vaccine, mostly due to increased injection site adverse experiences.

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Introduction

Cervical cancer is the second leading cause of death attributable to cancer among women worldwide, and more than 99% of all cervical cancers contain HPV DNA.¹ The well-established causal link between HPV and cervical cancer and the high prevalence of HPV infection has led to the development of prophylactic vaccines directed against the most common, high-risk oncogenic HPV types.² Data suggest that within 3 years after initiation of sexual activity, up to 48% of women will have evidence of cervical human papillomavirus (HPV) infection.³

Phase III trials conducted in approximately 18,150 young adult women have demonstrated that a prophylactic quadrivalent (types 6/11/16/18) HPV L1 virus-like particle (VLP) vaccine was highly effective in preventing HPV 6-, 11-, 16- or 18-related cervical, vaginal and vulvar neoplasias (as well as anogenital condylomata) and persistent infection in women who were naïve to the respective vaccine HPV types at enrollment.^{4,5} Additionally, a bivalent HPV 16/18 VLP vaccine was shown to be effective in preventing persistent HPV16/18 infection among women naïve to HPV 16/18 prior to vaccination.⁶ However, the ability of prophylactic HPV vaccines to attenuate or abrogate disease in women who have persistent antibodies from a previous infection with a vaccine HPV type has not yet been defined.

This report presents the results of an analysis of data from three randomized, double-blind, placebo-controlled clinical trials to investigate the prophylactic efficacy of the quadrivalent HPV vaccine against disease related to HPV 6, 11, 16 or 18 in subjects who have previously been infected with ≥ 1 vaccine HPV type. This analysis was conducted to determine whether subjects with serological evidence of past HPV 6, 11, 16 or 18 infection, but with no evidence of current HPV 6, 11, 16 or 18 cervical/anogenital infection (with the same HPV type) benefit from vaccination with quadrivalent HPV vaccine. These data will also address the tolerability of vaccination in subjects who have previously been exposed to a vaccine HPV type, and remain seropositive to that type.

Results

Baseline demographic characteristics between subjects HPV PCR negative and seropositive for HPV 6/11/16/18 and the overall trial population can be seen in Table 2. In general, subjects seropositive at baseline had a higher mean number of sexual partners. These subjects also had a higher incidence of past pregnancy, and a history of chlamydia infection roughly double that of the overall population. Seropositive subjects were also more likely to be diagnosed with low-grade squamous intraepithelial lesions (LSIL) at enrollment.

In the overall population, 8.1%, 2.0%, 11.3% and 3.7% of subjects were seropositive to HPV 6, 11, 16 and 18 at enrollment, respectively (Table 3) (without respect to HPV DNA status). The majority of subjects who had antibodies to a specific vaccine HPV type at baseline were DNA negative to that HPV type as determined by PCR analysis, though a higher percentage of

HPV 16 DNA positivity was seen in comparison to the other HPV types. In total, 6.4%, 1.8%, 6.9% and 2.7% of subjects were seropositive and PCR negative to HPV 6, 11, 16 and 18, respectively. The proportion of seropositive and PCR negative women was balanced between vaccine and placebo groups for all vaccine HPV types.

Vaccine efficacy against HPV 6/11/16/18-related CIN 1 or worse in subjects seropositive and DNA negative to the relevant HPV type at baseline was 100% (95% CI: 28.7, 100) (Table 4). No vaccinated subjects developed cervical disease due to an HPV type with which they had previously been infected. Seven subjects receiving placebo developed cervical disease due to one of these types. Six of these cases were related to HPV 16 and one was related to HPV 18. Efficacy against the incidence of HPV 6/11/16/18-related external genital lesions in subjects seropositive and DNA negative to the relevant HPV type at baseline was also 100% (95% CI: 39.5, 100) (Table 5). Again, no cases were seen amongst vaccinated subjects, while there were eight placebo subjects who developed external genital disease related to a vaccine HPV type with which they had previously been infected. Five of these cases were related to HPV 6, two were related to HPV 16, and one related to HPV 18. Details of women diagnosed with CIN or EGL can be seen in Figure 1.

Subjects in the detailed safety population ($n = 948$) (filled out vaccine report cards) given vaccine reported slightly more adverse experiences when compared to those given placebo (92.5% vaccine versus 85.8% placebo) (Table 6). This difference was due predominantly to injection-site adverse experiences (84.1% vaccine versus 75.3% placebo). Serious vaccine-related adverse experiences included gastroenteritis, headache and hypertension (in the total safety population), and bronchospasm (in the detailed safety population).

Discussion

In the current analysis, we examined the data from a population of subjects who were previously infected with a vaccine HPV type (seropositive and DNA negative at baseline) prior to enrolling in a quadrivalent HPV vaccine clinical trial. Subjects were followed for an average of 40 months. Seven subjects in the placebo group developed cervical disease related to a vaccine HPV type they had previously encountered. Out of these seven vaccine type related cases, six were due to HPV 16, 1 was due to HPV 18. Non-vaccine high-risk HPV types were found in 2 cases of HPV 16 related disease (16 + 58; 16 + 33) and one case of HPV 18 related disease (18 + 33 + 52 + 56). Eight subjects in the placebo group developed HPV-related external anogenital lesions, (Condyloma, VIN or VaIN) related to a vaccine HPV type they had previously encountered. Out of these eight EGLs, five were due to HPV 6, two were due to HPV 16 and 1 was due to HPV 18. No non-vaccine types (out of 10 tested types) were found. No subject receiving HPV 6/11/16/18 vaccine developed cervical or external genital disease related to a vaccine HPV type to which they were seropositive and DNA negative at enrollment (vaccine efficacy: 100% [cervical 95% CI: 28.7, 100.0; external anogenital 95% CI: 39.5, 100.0]).

