Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16, 18) vaccine

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**KEYWORDS**
Human papillomavirus; Immunogenicity; Vaccines; Virus-like particles; Cervical cancer; Cervical intraepithelial neoplasia; Genital warts

**Summary**
*Background:* Human papillomaviruses (HPVs) play an obligatory role in cervical cancer development. Thus, immunization of women using a prophylactic vaccine against the most common high-oncogenic risk types (e.g., HPV 16 and 18) and HPV 6 and 11, which contribute to development of low-grade cervical lesions and cause most anogenital warts, represents a logical primary prevention strategy.

*Perspectives:* At the time of licensure, Phase II/Phase III studies showed that administration of a quadrivalent HPV (types 6, 11, 16, 18) vaccine to young women (16 to 26 years) naïve to the vaccine HPV types resulted in 100% efficacy against HPV 16- and 18-related precancerous cervical lesions, 100% efficacy against HPV 16- and 18-related high-grade vulvar/vaginal neoplasias, 95% efficacy against HPV 6, 11, 16, or 18-related cervical intraepithelial neoplasia/adenocarcinoma in situ, and 99% efficacy against HPV 6, 11, 16, or 18-related genital lesions. The quadrivalent HPV vaccine is highly immunogenic in adolescent males and females, and long-term follow-up of young women did not detect evidence of waning immunity through 5 years.

*Conclusions:* The quadrivalent vaccine is generally well tolerated. The efficacy and safety of the quadrivalent vaccine is continuing to be investigated in young men and mid-adult women. Nordic cancer registries are providing ongoing long-term pharmacovigilance.

**Introduction**
Human papillomaviruses (HPV) infections, which are very common among sexually active women, are linked not only to development of genital neoplasias, such as cervical, vulvar, vaginal cancers, but also to high-grade (cervical intraepithelial neoplasias [CIN] 2/3) and low-grade cervical lesions (CIN 1), anogenital warts, and vulvar/vaginal dysplasia. Recent worldwide estimates indicate that HPV-related infection causes 470,000 cases of cervical cancer and claims the lives of about 250,000 women per year, a large proportion of which occurs in developing countries, where cervical screening programs using the Papanicolaou (Pap) test are limited or absent.

In light of the central and obligatory role that HPV plays in the development of cervical cancer, immunization of women using a vaccine directed against the most common high-oncogenic risk HPV types (e.g., HPV 16 and 18) represents a logical primary prevention strategy to reduce the occurrence of this devastating disease.

The purpose of this article is to review the clinical development, efficacy and safety results for a recombinant
quadrivalent HPV vaccine in young women and adolescent males and females, and to describe ongoing clinical trials evaluating its efficacy in young men and mid-adult women (26–45 years of age). The focus of the article is on clinical efficacy in terms of preventing clinical disease caused by HPV 6, 11, 16, and 18. For a detailed review of the ability of quadrivalent vaccine to induce high, persistent anti-HPV titers in young women and in male and female adolescents, the reader is directed to the article on immunogenicity by Dr. Frazer (this supplement).

Rationale for developing and composition of a quadrivalent HPV L1 VLP vaccine

As reviewed in detail in the article by Dr. Paavonen (this supplement), most HPV-related disease can be attributed to HPV types 6, 11, 16, and 18. HPV types 6 and 11 are linked to development of nearly 90% of all anogenital warts in women and men and approximately 10% of low-grade cervical lesions. HPV 16 and 18 are responsible for approximately 70% of cervical cancers, 70% of other genital cancers in women, and approximately 85% of anal cancers. In addition, HPV 16 and 18 are associated with approximately 25% of low-grade cervical lesions and 50% of high-grade cervical lesions. Men develop anal or genital lesions related to HPV 16 and 18, and also contribute to the risk of cervical cancer in their partners by serving as carriers or vectors of HPV. Immunizing both women and men, therefore, with a prophylactic quadrivalent HPV vaccine targeting these common, major HPV types will result in substantial reductions in acquisition of HPV infection and the global burden of HPV-related disease.

The quadrivalent vaccine comprises a mixture of 4 types of virus-like particles (VLPs) derived from the major capsid protein L1 of HPV 6, 11, 16, and 18. These type-specific L1 VLPs are generated in culture using recombinant technology in the yeast Saccharomyces cerevisiae, and after purification, are adsorbed onto the adjuvant amorphous aluminum hydroxyphosphate sulfate. The quadrivalent vaccine is administered by intramuscular injection (0.5 mL injection volume containing 225 µg of aluminum adjuvant) in three doses within 6 months (day 1, month 2, and month 6). Yeast-derived vaccines have been successfully employed to produce many other vaccines, including hepatitis B vaccine, and have been generally safe and well-tolerated when administered to millions of children and adults worldwide.

Quadrivalent HPV vaccine clinical development program

As summarized in Figure 1, the quadrivalent HPV vaccine clinical development program is comprehensive and, to date, has involved the participation of more than 30,000 subjects in 33 countries. The goal was to include subjects with a broad range of ethnic backgrounds, sexual behaviors, and concomitant diseases, thereby allowing generalization to the overall population. Two Phase II studies, both in women 16–23 years of age, have been conducted, including a proof-of-principle study evaluating a monovalent HPV 16 vaccine and a dose-ranging study (protocol 007) of the quadrivalent vaccine. Follow up of women in the latter study was extended beyond the initial design of 36 months, permitting efficacy evaluation up to 5 years after the first immunization.

Data from two ongoing, randomized, double-blind, placebo-controlled, multicenter Phase III studies have been evaluated (approximately two years of follow-up at the time of licensure): the Females United to Unilaterally Reduce Endo/Ectocervical disease (FUTURE I) and FUTURE II. In total, these phase III studies enrolled more than 17,000 nonpregnant young women (16 to 23 years of age)
and plan to include follow up visits over a period of 4 years. The studies evaluated the efficacy of a quadrivalent vaccine in reducing the incidence of HPV 6-, 11-, 16- and 18-related CIN 1, CIN 2/3, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), vaginal cancer, vulvar cancer, AIS, cervical cancer, and external genital warts. In addition, the duration of vaccine efficacy beyond the planned end of the primary efficacy trial is being extended in a subset of women enrolled in the Nordic region (Nordic Cancer Registry Extension).

An additional Phase III study that has been completed compared the immunogenicity and tolerability of a quadrivalent HPV vaccine in adolescent boys and girls to those in women 16–23 years of age. This study showed that higher anti-HPV (types 6, 11, 16, and 18) antibody levels occurred in adolescent males and females compared with adult women and supported bridging the efficacy findings from older adolescents and young adult women to young adolescents. Further discussion of this study can be found in the review by Dr Frazer (this supplement). Two additional Phase III studies were initiated in 2004 (due to be completed in 2009) in order to evaluate the efficacy of the quadrivalent vaccine in mid-adult women 26–45 years and in 16–23 old males.

Choice of appropriate clinical endpoint to evaluate HPV vaccine efficacy in preventing cervical cancer

A key aspect of the clinical efficacy studies of prophylactic HPV vaccines in women has been the utilization of CIN 2/3 as a surrogate marker for cervical cancer. While the primary goal of any HPV vaccine is to reduce the occurrence of cervical cancer, ethical, sample size, and time considerations make it imperative to use an appropriate and meaningful surrogate endpoint for clinical efficacy evaluations.

Several clinical conditions could potentially serve as surrogate endpoints, including persistent HPV infection, CIN 1, and CIN 2/3. However, only cervical biopsy-confirmed CIN 2/3 meets all of the key criteria for a robust, reliable, and clinically relevant endpoint to test HPV vaccine efficacy. This is because: 1) CIN 2/3 is an obligate precursor for, and is closely temporally associated with, the development of cervical cancer; 2) CIN 2/3 is a clinically important syndrome requiring treatment; and 3) a reduction in incidence of CIN 2/3 implies a reduced risk of cervical cancer. Thus, expert committees convened by the World Health Organization and the United States Food and Drug Administration recommended that CIN 2/3 be employed as the definitive endpoint to measure the efficacy of an HPV vaccine efficacy.25

Efficacy of a quadrivalent HPV vaccine

Phase II dose-ranging study

A double-blinded, placebo-controlled, dose-ranging study of the quadrivalent vaccine was conducted in 1,106 women 16–23 years of age with the objective of guiding dose selection for subsequent Phase III studies and to determine efficacy in preventing persistent HPV infection and disease related to HPV 6, 11, 16, and 18. Women naive to the relevant HPV type at baseline received in a randomized manner 1 of 3 preparations of the quadrivalent vaccine or placebo, administered by intramuscular injection at Day 1, Month 2, and Month 6. The following doses for the HPV vaccine were used:

- **Group 1:** 20 µg type 6, 40 µg type 11, 40 µg type 16, and 20 µg type 18;
- **Group 2:** 40 µg type 6, 40 µg type 11, 40 µg type 16, and 40 µg type 18;
- **Group 3:** 80 µg type 6, 80 µg type 11, 40 µg type 16, and 80 µg type 18.

An interim safety and immunogenicity analysis used as the primary end point the type-specific immune response at Month 7, corresponding to approximately the peak anti-HPV responses, showed that the lowest vaccine dose induced serological antibody responses comparable to the intermediate-dose and high-dose preparations. Following the interim analysis, the study focused on evaluating the efficacy of the low-dose formulation, which was ultimately chosen for Phase III studies.

In women who received the quadrivalent vaccine, the combined incidence of persistent HPV 6, 11, 16, or 18 infection or related cervical and genital disease over the 30 months of follow-up was decreased by 90% (95% CI, 71–97%) compared with women receiving placebo. Considering CIN and genital warts as a single endpoint, the quadrivalent vaccine was 100% effective (P = 0.0151) in HPV-naive women. None of the patients receiving vaccine and 6 patients receiving placebo developed HPV 6-, 11-, 16-, or 18-related cervical and genital disease over 30 months. The high efficacy of the vaccine was sustained over 5 years, as evidenced by an extended follow up of 241 patients.21 At 5 years, the vaccine prevented 96% or 100% of HPV 6, 11, 16, or 18 infection or cervical and genital disease, respectively (Table 1). These findings demonstrate that a quadrivalent vaccine substantially reduces the acquisition of infection and clinical disease caused by these common HPV types with an efficacy similar to that with currently available vaccines, including the polyvalent pneumococcal vaccine and polio vaccines.26,27

All women receiving quadrivalent vaccine developed detectable neutralizing antibodies to HPV 6, 11, 16, and 18 at completion of the vaccine regimen at Month 7 (see review by Dr. Frazer). Geometric mean titers of vaccine-induced antibodies peaked at Month 7 and thereafter gradually declined, reaching a plateau at Month 24. In addition, women vaccinated with the quadrivalent vaccine exhibited immune memory at five years of follow-up, as demonstrated by a marked anamnestic response.28

Combined Phase II/III analysis

To further define the efficacy of the quadrivalent vaccine efficacy against HPV-related external genital lesions, a combined Phase II and III efficacy analysis was performed that involved more than 20,000 women ranging in age from 16 to 26 years and spanned Europe, North America, Latin America and Asia Pacific region.29,30 Table 2 summarizes the principal design features of studies included in the
Table 1  Per-protocol efficacy results from a Phase II study (Protocol 007) comparing quadrivalent (HPV types 6, 11, 16, and 18) vaccine with placebo (all subjects through 3 years and extension subjects over 5 years). Data extracted from Villa et al.21

<table>
<thead>
<tr>
<th>HPV 6, 11, 16 or 18-related</th>
<th>Quadrivalent vaccine (N = 277)</th>
<th>Placebo (N = 275)</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>235</td>
<td>233</td>
<td>95.6%</td>
<td>(83.3, 99.5)</td>
</tr>
<tr>
<td>Disease</td>
<td>235</td>
<td>233</td>
<td>100%</td>
<td>(12.4, 100)</td>
</tr>
<tr>
<td>CIN 1, 2 or 3</td>
<td>235</td>
<td>233</td>
<td>100%</td>
<td>(&lt;0, 100)</td>
</tr>
<tr>
<td>Condyloma</td>
<td>235</td>
<td>233</td>
<td>100%</td>
<td>(&lt;0, 100)</td>
</tr>
</tbody>
</table>

A subset (241 subjects) had follow-up through 5 years post-dose 1.
* 1 case of confirmed persistent infection: HPV 18 DNA detected at months 12 and 18 only. 1 case of HPV 16 DNA detected at the last visit (month 36).

Table 2  Design overview of principal studies evaluating the safety and efficacy of a quadrivalent vaccine in young women

<table>
<thead>
<tr>
<th>Design feature</th>
<th>Villa et al. 2005 (Protocol 007)18</th>
<th>FUTURE I22</th>
<th>FUTURE II23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>550</td>
<td>5,746</td>
<td>12,157</td>
</tr>
<tr>
<td>Study sites</td>
<td>International, multicenter</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td>Double-blind</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study vaccine</td>
<td>Quadrivalent vaccine or placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination regimen</td>
<td>0, 2, 6 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit schedule after vaccination</td>
<td>Every 6 mos for 3 yrs</td>
<td>Every 6 mos, for 4 years</td>
<td>Yearly for 4 years</td>
</tr>
<tr>
<td>Age</td>
<td>16–23 yrs</td>
<td>16–23 yrs</td>
<td>15–26 yrs</td>
</tr>
<tr>
<td>Number of lifetime male sex partners</td>
<td>0 to 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous history of HPV-related disease</td>
<td>Not allowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytological abnormalities or HPV infection at enrollment</td>
<td>Allowed</td>
<td>Subjects with visible genital warts were not enrolled</td>
<td></td>
</tr>
<tr>
<td>Requirement for biopsy</td>
<td>All abnormal areas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology interpretation</td>
<td>Routine in central lab; endpoint determined by blinded expert pathology panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV causality assessment</td>
<td>PCR assay on frozen biopsy specimens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Protocol 005 results20 involving 2391 16–23-year-old women were also included in HPV 16 specific results.

combined analysis (i.e., FUTURE I and II as well as Phase II protocol 007). In addition, results from protocol 005,20 which involved immunization of 2391 women, 16–23 years old, with a monovalent HPV 16 L1 VLP vaccine, were also included in the HPV 16-specific results. The combined data presented in this review is based on an analysis conducted at the time of vaccine licensure (i.e., approximately 2 years of post-vaccination follow-up). These values differ slightly from the final published combined analyses, which presents 3-year data.

The primary analytical end point was the combined incidence of HPV 16/18-related CIN 2/3, AIS, or cancer (as determined by a study pathology panel that was blinded to HPV DNA results and vaccine allocation). This primary analysis involved the per-protocol population – that is, subjects who had no serum antibodies to HPV 16 or 18 at day 1, had no HPV 16 or 18 DNA in their swabs at day 1 through month 7, and had completed 3 vaccinations). However, additional, prespecified secondary analyses were performed utilizing a modified intention-to-treat population – that is, women who received ≥1 dose of vaccine and were HPV 16/18 negative at day 1. This population more closely resembles real-life settings than the rigidly defined per protocol cohort.

Overall, 73% of enrolled women on day 1 tested negative for HPV types 6, 11, 16, 18 and 27% tested positive to at least one HPV type. The relative prevalence rates per HPV type occurred in the order HPV 16 > HPV 6 > HPV 18 > HPV 11, a finding generally consistent with epidemiologic data. The two study groups (quadrivalent vaccine and placebo) were similar with respect to HPV-associated disease at baseline regardless of the type of analysis performed (per protocol or modified intention-to-treat). As shown in Table 3, approximately 11% of both study groups had a
and vulvar or vaginal neoplasias (Figure 2). 29, 30

18-related cases of genital lesions, including genital warts
cervical lesions related to HPV 16 and 18 (Figure 2). This analysis also showed that the
one cytological abnormality at baseline, the vast majority of
cervical lesions related to HPV 16 and 18 during the vaccination period or who violated
LSIL = low-grade squamous intraepithelial neoplasia, HSIL = high-grade squamous intraepithelial neoplasia, AGC = atypical glandular cells.

ASCUS or ASC-H cannot exclude HSIL, LSIL = low-grade squamous intraepithelial neoplasia, HSIL = high-grade squamous intraepithelial neoplasia, AGC = atypical glandular cells.

Table 3 Abnormal cervical cytology at enrollment in the combined Phase II and III analysis of efficacy studies

<table>
<thead>
<tr>
<th>Day 1 Pap test diagnosis</th>
<th>Quadrivalent vaccine (N = 9087)</th>
<th>Placebo (N = 9087)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cytological abnormality</td>
<td>11.5%</td>
<td>11.3%</td>
</tr>
<tr>
<td>ASCUS</td>
<td>4.5%</td>
<td>4.7%</td>
</tr>
<tr>
<td>ASC-H</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>LSIL</td>
<td>5.9%</td>
<td>5.7%</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>AGC</td>
<td>0.066%</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

ASCUS = atypical squamous cell of unknown significance, ASC-H = atypical squamous cells – cannot exclude HSIL, LSIL = low-grade squamous intraepithelial neoplasia, HSIL = high-grade squamous intraepithelial neoplasia, AGC = atypical glandular cells.

% based on number of subjects with indicated diagnosis/number of subjects with a satisfactory Day 1 Pap test result multiplied by 100.

cytological abnormality at baseline, the vast majority of which could be categorized as LSIL or ASCUS.

At the time of licensure, in young women naïve to HPV 16 and 18 until completion of the vaccination regi-
men, the combined Phase II/Phase III per-protocol analysis demonstrated that prophylactic quadrivalent HPV vaccina-
tion was 100% efficacious against high-grade precancerous and noninvasive cancerous cervical lesions related to HPV 16 and 18 (Figure 2). This analysis also showed that the quadrivalent vaccine prevented 100% of HPV 16- and HPV 18-related cases of high-grade (grade 2/3) vulvar or vaginal neoplasias, 95.2% of HPV 6, 11, 16, or 18-related cases of CIN (grades 1, 2/3) or AIS and 99.1% of HPV 6, 11, 16, or 18-related cases of genital lesions, including genital warts and vulvar or vaginal neoplasias (Figure 2). 29, 30

Similarly, in the modified intention-to-treat cohort, a broader group that included all of the women in the per
protocol group plus women who became infected with HPV 16 or HPV 18 during the vaccination period or who violated
the protocol by missing some protocol visits or vaccine doses, the quadrivalent vaccine was still 98.8% efficacious against high-grade precancerous and noninvasive cancerous cervical lesions related to HPV 16 and 18 (Figure 2). In addition, the quadrivalent vaccine prevented 100% of HPV 16- and HPV 18-related cases of high-grade (grade 2/3) vulvar or vaginal neoplasias, 93.7% of HPV 6, 11, 16, or 18-related cases of CIN (grades 1, 2, 3) or AIS and 94.8% of HPV 6, 11, 16, or 18-related cases of genital lesions including genital warts and vulvar or vaginal neoplasias (Figure 2).

The combined Phase II/III study population at baseline included women who were naïve to HPV 6, 11, 16, and 18 as well as women who had been previously exposed to these specific types, as determined by serology testing for presence of HPV type-specific antibodies or polymerase chain reaction (PCR) testing of genital samples for the presence of HPV DNA. Thus, it is possible to examine broad trends in efficacy in preventing HPV 6/11/16/18-related disease in several groups of patients categorized according to whether they were HPV DNA positive by PCR or seropositive to the particular vaccine HPV types at baseline. The quadrivalent vaccine was 100% effective in reducing the incidence of HPV 6/11/16/18-related disease in HPV-naïve women (i.e., seronegative and HPV DNA negative by PCR) as well as in women who had been previously exposed to at least 1 vaccine HPV type at enrollment, but had no ongoing HPV infection (i.e., seropositive but HPV DNA negative by PCR). However, there was no clear evidence of protection from disease cause by HPV types for subjects that were HPV DNA positive by PCR and/or seropositive at baseline. 31

Safety

The combined quadrivalent HPV vaccine safety database indicated that the quadrivalent vaccine was generally well tolerated in both young women and adolescents, as assessed using vaccination-report card (VRC)-aided surveillance for 14 days following each vaccine injection (Table 4). 32 The most common vaccine- or placebo-related systemic adverse experiences were fever (10.3% vs 8.6%), nausea (4.2% vs 4.1%), and dizziness (2.8% vs 2.6%), respectively (Table 4). Vaccine-related injection site adverse experiences included pain, swelling, erythema, and pruri-
tus, all of which occurred at a somewhat higher frequency than in subjects receiving aluminum-containing placebo (Table 4). Serious adverse experiences were reported in 102 of 21,464 total subjects who received both quadrivalent vaccine and placebo (including 9-26-year-old girls and women and 9-15-year-old boys). The most frequently reported serious adverse experiences in subjects receiving quadrivalent vaccine and placebo were headache (0.03% vs 0.02%, respectively), gastroenteritis (0.03% vs 0.01%), appendicitis (0.02% vs 0.01%), and pelvic inflammatory disease (0.02% vs 0.01%), but none was considered to be related to vaccine components. 32

Adverse event data from the Phase III adolescent immunogenicity substudy showed that the quadrivalent vaccine was generally well tolerated in young adolescent girls or boys, as well as in older adolescent and young adult females. 24 All systemic adverse events and vaccine-related systemic events occurred with a similar frequency in these groups. The younger groups (boys and girls aged 10 to 15 years) had slightly fewer injection site adverse reactions compared with adult women, although febrile episodes (oral temperature ≥37.7°C) over the first 15 days following vaccine administration occurred more often in boys and girls than in young women aged (12.8–13.8% vs. 7.3%, respectively). 24 However, these fevers resolved quickly without any complications.
Figure 2. Combined analysis (per-protocol [top] and modified intention-to-treat [bottom]) of Phase II and III clinical studies at the time of vaccine licensure comparing effects of quadrivalent HPV vaccine with placebo on the occurrence of high-grade precancerous genital lesion or adenocarcinoma in situ and external genital lesions (vulvar, vaginal intraepithelial neoplasia and genital warts) in young women. Percentage reductions are shown with 95% CI in parentheses. The first endpoint (HPV16/18-related CIN 2/3 or AIS) included data from protocol 005 (monovalent vaccine), protocol 007, and FUTURE I and II; all other endpoints included protocol 007, FUTURE I and II only. CIN = cervical intraepithelial neoplasia, VIN = vulvar intraepithelial neoplasia, AIS = adenocarcinoma in situ, VaIN = Vaginal intraepithelial neoplasia.

Evaluation of pregnancy outcomes included the medical history during the pregnancy, mother and child’s outcomes in the neonatal period, causes of spontaneous abortion, and elective termination. Infants were followed to the end of studies to look for late events not detected in the neonatal period. At the time of licensure, a total of 2266 subjects became pregnant during clinical trials (vaccine = 1115, placebo = 1151), even though subjects were instructed to use contraception during the vaccination phase of the study. Of these pregnancies, the percentage of subjects experiencing an adverse outcome was comparable in the vaccine or placebo groups. The proportion of pregnant women experiencing a serious adverse experience (the most common being premature onset of labor, conditions resulting in Caesarean section, and pregnancy-related medical problems) was also 3.6% in both groups.
The rates of congenital abnormalities were comparable to those in the general population and similar between the quadrivalent HPV vaccine (15 cases) and the placebo group (16 cases). However, it is recommended that pregnancy be avoided during the course of vaccination. Through the central Nordic registry, long-term efficacy and safety is continuing to be evaluated on a population basis in real time and will include monitoring general safety and pregnancy outcomes.

Ongoing studies with quadrivalent HPV vaccine

An ongoing study in the Phase III clinical development program for the quadrivalent HPV vaccine is evaluating the immunogenicity and tolerability of the vaccine in men 16 to 23 years old; results are expected towards the end of 2007. Genital warts occur in both sexually active men and women, and a majority (85%) of anal cancer cases worldwide can be attributed to HPV infection. Therefore, it is appropriate to test the potential impact and benefits of administering a quadrivalent HPV vaccine in males. This is particularly germane in light of the lack of success of other vaccination programs that targeted females only. For example, selective immunization of schoolgirls, susceptible women after pregnancy, and women at special risk had limited success in preventing rubella-induced malformations; in contrast, a program immunizing both boys and girls at the ages of 18 months and 12 years against measles, mumps, rubella vaccination (MMR) ultimately led to complete eradication of the rubella syndrome. An additional Phase III study is being conducted in mid-adult women aged 24 to 45 years of age. This placebo-controlled, triple-blinded study is following a total of 2800 subjects over a 3-year period (with Pap screening, HPV DNA testing, and genital inspections every 6 months) in order to evaluate the safety profile of the quadrivalent vaccine and its efficacy in preventing HPV types 6-, 11-, 16-, and 18-related infections and disease. This is an important study since women remain at risk of HPV infection throughout their life.

Conclusions

The quadrivalent (HPV types 6, 11, 16, 18) vaccine is formulated to protect against the most common disease-causing HPV types and is expected to reduce substantially the morbidity, mortality, and cost burden of HPV infection. The quadrivalent vaccine has demonstrated high efficacy in HPV-naive women against anogenital cancers by preventing HPV 16/18-related CIN 3/AIS (cervical cancer), HPV 16/18-related VIN 2/3 and VaIN 2/3 (vulvar/vaginal cancer), CIN (all grades), as well as external genital lesions (VIN, VaIN and genital warts) caused by HPV types 6, 11, 16, 18. In adolescent males and females, and young women the quadrivalent HPV vaccine was found to be immunogenic and safe, with a tolerability profile comparable to placebo. Long-term follow up of young women provide no evidence of waning immunity through 5 years, as evidenced by high efficacy for prevention of persistent infection and disease caused by HPV 6, 11, 16 or 18. Based on these very positive results, more than 60 countries, including the United States and European Union, have approved the quadrivalent vaccine for clinical use. As part of the Phase III clinical development program, the efficacy and safety of the quadrivalent HPV vaccine is continuing to be investigated in young men and mid-adult women.

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Conflict of Interest statement

Dr. Villa has received honoraria from Merck Research Laboratories that were given for consultation work and membership in the Phase III HPV Vaccine Steering Committee during the past three years.

References


34. Bottiger M, Forsgren M. Twenty years’ experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old girls and of women postpartum) and 13 years of a general two-dose vaccination. Vaccine 1997;15:1538-44.