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Cervarix™

Human Papillomavirus Vaccine

580299
HPV-16/18 VLP AS04
HPV-16/18 AS04
HPV-16/18 L1 AS04

Human papillomavirus vaccine types 16 and 18 (recombinant, AS04 adjuvanted)

Human papillomavirus (HPV) 16/18 L1 virus-like particle (VLP) vaccine formulated with AS04 adjuvant

EN: 309201

Abstract

Cervarix™ is a bivalent virus-like particle (VLP) vaccine adjuvanted with monophosphoryl lipid A and alum, designed to provide protection against infection with genital tract human papillomaviruses (HPVs) types 16 and 18, which account for over 70% of cervical cancers. A phase II study and an interim analysis of a phase III study showed that Cervarix™ is safe and well tolerated in young women aged 15-25 years. In both studies, the vaccine was highly immunogenic (100% seroconversion rates) and after 4.5 years of follow-up, vaccine-induced antibody titers were over 14-17-fold higher than those noted for natural infection. The efficacy of Cervarix™ for preventing persistent HPV-16 and/or -18 infection at the cervix was 80-94%. Cervarix™ also provided significant cross-protection against infection with genetically closely related HPV types 31 and 45. Interim analysis of the phase III study indicated that the efficacy of Cervarix™ in preventing HPV-16/18-related cervical intraepithelial neoplasia (CIN) grade 2/3 may be as high as 100%.

Background

The pathogenic potential of human papillomaviruses (HPVs) was recognized and documented in the late 1970s and subsequent years, when it became possible to clone the viral genomes from pathological tissues of humans and animals. Papillomaviruses cannot be grown in conventional tissue cultures, necessitating molecular techniques for viral diagnosis. The genomes of over a hundred HPVs have been described to date and they naturally fall into two groups, the mucosal HPVs and the cutaneous HPVs. All but 2 of the approximately 40 mucosal HPVs are infections of the genital tract.

Genital tract HPV infections are transmitted sexually and are very common. Most of the infections are asymptomatic and harmless, but in a minority of infected individuals they cause benign or malignant disease. Worldwide, cancers attributable to genital tract HPVs include cancer of the cervix (100% of about 500,000 cases), cancer of the vulva and vagina (about 40% of 40,000 cases), cancer of the anus (about 90% of 30,000 cases), cancer of the penis (about 40% of 26,000 cases) (1) and cancer of the oropharynx (about 50% of 52,000 cases) (2).

The double-stranded DNA HPV genome is about 8,000 base pairs in size. The oncogenic effect of HPVs is mediated by the *E6* and *E7* oncogenes, which are invariably expressed in the nuclei of cells of tumors caused by HPV. The major capsid protein L1 of HPVs is the immunogen in prophylactic HPV vaccines designed to prevent HPV infections. Initially, it had seemed that it would be difficult to develop a vaccine that would prevent a mucosal genital tract infection, but studies in rabbits, dogs and cattle with the respective papillomaviruses showed that immunization with the major capsid protein provided protection against subsequent challenge with the virus (3-5). The major capsid protein L1 of HPVs, when expressed in yeast or baculovirus systems, self-assembles into virus-like particles (VLPs).

Cervarix™ is a bivalent vaccine designed to provide protection against infection with genital tract HPV types 16 and 18. HPV-16 is estimated to be responsible for a little over 50% of cervical cancers and for a higher proportion of HPV-associated cancers at other sites (6). HPV-18 is estimated to be responsible for about 18% of cervical cancers and for a lower proportion of cancers at other sites (6).

Cervarix™ is a bivalent HPV-16/18 L1 VLP vaccine. Each dose of the vaccine contains 20 μg each of HPV-16

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and -18 L1 proteins self-assembled as VLPs and adjuvanted with AS04 (50 μg of 3-*O*-desacyl-4'-monophosphoryl lipid A [MPL] adsorbed onto 500 μg of aluminum hydroxide). The vaccine antigens are produced using a baculovirus expression vector system in which each type of VLP is produced in *Spodoptera frugiperda* Sf9 cells and an Hi-5 cell line derived from *Trichoplasia ni.* AS04 combines the adjuvant activity of alum and MPL, a nontoxic derivative of lipopolysaccharide (LPS). The adjuvant capacity of AS04 has been evaluated during the development of several candidate vaccines, including hepatitis B, herpes simplex and HPV-16/18 L1 VLPs. Vaccination of animals and human subjects with an AS04-formulated HPV-16/18 VLP vaccine has been shown to induce higher total anti-L1 VLP16 and -L1 VLP18 antibody responses than an alum-only formulation (7). The vaccine is supplied in individual 0.5-ml prefilled syringes and administered into the deltoid muscle on a 0-, 1- and 6-month schedule.

Clinical Studies

A double-blind, multicenter, randomized, placebo-controlled phase II clinical trial assessing the safety, immunogenicity and efficacy of Cervarix™ against incident and persistent HPV-16 and/or -18 (16/18) infections and their associated cytological and histological outcomes is ongoing (8). A total of 1,113 healthy women aged 15-25 years were enrolled and randomized from 32 study sites in North America (Canada and the U.S.) and Brazil; 560 women received vaccine and 553 received placebo. Women were eligible for the study if they had had no more than 6 sexual partners, no history of an abnormal Pap test or of ablative or excisional treatment of the cervix, and no ongoing treatment for condylomata. Women with DNA from one or more high-risk HPV types or an abnormal cytology detected at a screening visit within 90 days before the initial study visit were not enrolled. Vaccine safety, immunogenicity and efficacy were evaluated after 18-27 months of follow-up. Women who received all three doses of vaccine (n=393) or placebo (n=383) were invited to participate in an extended follow-up study, which is currently ongoing (9).

Cervical specimens were obtained for cytology and HPV DNA testing at screening and every 6 months thereafter. In addition, at months 0 and 6 and subsequently every 3 months up to 27 months, women self-obtained cervicovaginal samples for HPV DNA testing. Cytology results were reported according to the Bethesda classification system by a central laboratory. Colposcopy was performed after two reports of atypical squamous cells of undetermined origin (ASCUS) or low-grade squamous cell intraepithelial lesion (LSIL), or a single report of a higher grade cytological abnormality. A panel of three pathologists made a consensus diagnosis for HPV-16- and HPV-18-associated lesions according to the cervical intraepithelial neoplasia (CIN) classification. HPV DNA detection was performed for 14 high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and 11 low-risk types (6, 11, 34, 40, 42-44, 53, 54, 70 and 74) using the broad-spectrum PCR SPF10 primers with the line probe assay (LiPA). HPV-16 and -18 infections were confirmed by a type-specific PCR. The primary endpoint for evaluation of vaccine efficacy was incident HPV-16/18 infection. Secondary objectives were to assess vaccine efficacy in the prevention of persistent HPV-16/18 infection, cytological abnormalities associated with HPV-16/18 infection, histopathological abnormalities associated with HPV-16/18 infection, and incident infection associated with other high-risk types of HPV. Prevention of histopathological abnormalities independent of HPV DNA type was added as a *post hoc* objective.

An interim analysis of a double-blind, randomized, controlled phase III trial of Cervarix™ has also been published (10). A total of 18,644 women aged 15-25 years living in 14 countries (Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, the U.K. and the U.S.) were randomly assigned to receive either Cervarix™ (n=9,319) or a hepatitis A vaccine (n=9,325). Procedures for HPV DNA testing, cytology and clinical management were similar to those used in the above phase II trial. Cervical samples for cytology and DNA testing were collected every 6 months; self-obtained cervicovaginal samples were not collected. If DNA from several HPV types was detected in a lesion, attribution of causality for a particular type was based on the presence of that type in one of two preceding cytology samples. If the role of HPV-16 or HPV-18 was in question, immunohistochemical analysis was performed for type-specific *E4* gene expression. The primary endpoint for vaccine efficacy was prevention of CIN grade 2 or 3 associated with HPV-16/18 in women who were seronegative and DNA-negative for the corresponding vaccine type at month 0. Additional endpoints included CIN1+ associated with HPV-16/18, persistent infection with HPV-16/18 or other oncogenic HPV types (at 6 and 12 months).

In the phase II trial, the vaccine efficacy against incident HPV-16/18 infection, defined as at least one positive PCR result for HPV-16/18 from the cervicovaginal or cervical swab specimens, was 68% (confidence intervals are provided in Table I) among women in the intent-to-treat (ITT) cohort (all women who received at least one dose of vaccine and were negative for high-risk HPV DNA at month 0). If the analysis was based on the cervical swab samples, which were collected at longer time intervals, vaccine efficacy was 83%, most likely reflecting the short duration of many incident infections. When data from the extended follow-up were included in the analysis, the efficacy of Cervarix™ for preventing incident HPV-16/18 infection, detected in cervical swab samples, was 88% in the ITT cohort. In a preliminary report of women followed for up to 5.5 years, vaccine efficacy against incident HPV-16/18 infection was reported as 98% (95% confidence interval [CI], 89-100%).

The efficacy of the vaccine for preventing persistent HPV-16/18 infection after 27 months of follow-up was 87% and increased to 95% using data from the longer

Table I: Efficacy of Cervarix™ for preventing HPV-16/18 infection and related cervical disease in intent-to-treat (ITT) cohorts.

Endpoint	Trial	Follow-up (months)	Vaccine group		Placebo group		Efficacy % (95% CI)
			Total women	Total event	Total women	Total event	
Incident HPV-16/18, cervicovaginal/ cervical sample	Initial phase II	27	560	39	533	196	68 (49-79)
Incident HPV-16/18, cervical sample	Initial and extended phase II	53	481	9	470	73	88 (77-95)
Persistent HPV-16/18, cervicovaginal/ cervical sample	Initial phase II	27	560	4	533	31	87 (65-96)
Persistent HPV-16/18, cervical sample	Initial and extended phase II	53	481	1	470	16	94 (60-100)
Persistent HPV-16/18, cervical sample	Phase III	15	6344	38	6402	193	80 (70-87)
HPV-16/18 cytological abnormality, any grade	Initial and extended phase II	53	505	2	497	44	96 (83-99)
HPV-16/18 CIN2+	Phase III	15	7788	2	7838	21	90 (53-99)
HPV-16/18 CIN2+, additional analyses[1]	Phase III	15	7788	0	7838	20	100 (74-100)
High-risk HPV cytological abnormality, any grade	Initial and extended phase II	53	505	53	497	95	48 (27-63)
Incident HPV-45	Initial and extended phase II	53	528	1	518	17	94 (63-100)
Incident HPV-31	Initial and extended phase II	53	528	14	516	30	54 (11-78)

[1]In cases of mixed HPV infection, causality was established if a type was also detected in the preceding cytology samples and/or type-specific *E4* gene expression was detected in the lesion.

interval sampling. Inclusion of data from the extended follow-up resulted in a vaccine efficacy of 94% for prevention of persistent HPV-16/18 infection measured at the cervix with 6-month sampling. There was no difference in vaccine efficacy using a 6- or 12-month definition of persistent infection. The vaccine was equally effective for both HPV-16 and HPV-18 infections, although not all findings for HPV-18 were significant because of a limited number of events. In the interim 5.5-year analysis, presented at the 2007 American Association for Cancer Research (AACR) meeting, vaccine efficacy for prevention of 6-month persistent HPV-16/18 infection was 100% (95% CI, 81-100%). Estimates of vaccine efficacy were higher for according-to-protocol (ATP) analyses. The ATP analysis was restricted to women who fully complied with the study protocol and were cytologically negative, seronegative for HPV-16 and HPV-18 antibodies by ELISA, and HPV DNA-negative by PCR for high-risk HPV type. In the combined analysis of women in the initial 18-month and extended follow-up study, approximately 15% of women were excluded from analysis, with nearly half the exclusions due to serological evidence of prior HPV-16/18 infection. In the ATP cohort, vaccine efficacy was 95% for the prevention of incident HPV-16/18 infection and 100% for the prevention of persistent HPV-16/18 infection.

The interim efficacy analysis of the phase III study was done on the total vaccinated cohort, including women who received only one dose of vaccine. The mean length of follow-up at the time of the analysis was approximately 15 months. In women seronegative and DNA-negative for HPV, vaccine efficacy for prevention of persistent HPV-16/18 infection was 80%. Women with prevalent infection due to other HPV types or abnormal Pap smears caused by other HPV types were not excluded from the analysis. Of note, nearly all the infections were acquired before the three-dose vaccination course was completed.

A secondary endpoint for the phase II trial was cytology outcomes associated with HPV-16/18. The efficacy of Cervarix™ for preventing any-grade cytological abnormalites was 96% in the analysis of the ITT cohort of women in the combined initial and extended follow-up. Persistent HPV infection is considered an intermediate endpoint for HPV-related cervical cancer. For vaccine licensure, the U.S. FDA requires that prevention of histo-

logical changes indicative of HPV-related precancerous lesions of the cervix which are classified as CIN grade 2 or 3 be demonstrated. The interim analysis of the phase III trial was designed to provide an early and conservative estimate of vaccine efficacy for CIN2+ based on a modified ITT cohort. The analysis excluded women infected with the individual HPV type at study entry, but included those who had prevalent HPV infection or low-grade cytological abnormalities due to other HPV types at study entry and who received at least one vaccine dose. As noted above, the analysis was restricted to women both seronegative and DNA-negative for HPV-16/18. Cervarix™ showed 90% efficacy in the prevention of CIN2+ associated with the detection of HPV-16/18 DNA in the biopsy sample. The 2 cases of CIN2+ that were observed in vaccine recipients were probably not caused by HPV-16/18. In both cases, other oncogenic HPV types were also detected and HPV-16/18 was not detected in preceding cytology samples. The CIN2+ case in the vaccine group with HPV-18 could not be confirmed by type-specific PCR, and for both CIN2+ cases in the vaccine group, no *E4* gene expression could be detected in the lesion. After excluding these 2 cases from the analysis, vaccine efficacy was 100%. The vaccine had 89% efficacy for preventing CIN1+ associated with HPV-16/18, which increased to 96% after additional analysis to resolve the causality of mixed infection.

The phase II trial revealed a vaccine efficacy of 48% against abnormal cytological outcomes associated with any high-risk HPV type and vaccine efficacy against incident infection with HPV-45 and -31 of 94% and 54%, respectively. HPV-31 is genetically closely related to HPV-16, and HPV-45 is closely related to HPV-18. There was no significant protection against other genetically related types, such as HPV-33, -52 and -58. The recently reported analysis of the 5.5-year follow-up showed a slightly lower estimate of vaccine efficacy (38% against abnormal cytological outcomes; 88% and 53% for incident HPV-45 and-31 infections, respectively, and 15% against incident HPV-52 infection).

The interim analysis of the phase III trial included protection against persistent infection with other HPV types as an exploratory endpoint. Significant cross-protection against 6-month persistent infection was shown for HPV-45 (60%), HPV-31 (36%) and HPV-52 (32%). No analyses of protection against CIN2+ associated with oncogenic HPV other than vaccine types were reported.

In the phase II trial, 100% of women seroconverted to HPV-16-positive and HPV-18-positive by 7 months after three doses of vaccine. Titer values declined from peak responses 1 month after the third vaccine dose (study month 7) to a stable plateau beginning at month 18. Overall, there was a < 1 log decline in geometric mean titer (GMT) values from peak values to the end of follow-up at 51-53 months. Compared to titer values associated with naturally acquired HPV-16 and HPV-18 infection, vaccine-induced titers at 51-53 months were 17- and 14-fold higher, respectively. In the phase III study, among 6,979 women included in the immunogenicity analysis, 99.5% seroconverted for both HPV-16/18 after two or three doses of vaccine. After the third dose, peak immune responses of 9342 (95% CI, 8760-9961) ELISA units (EU)/ml for HPV-16 and 4769 (95% CI, 4491-5065) EU/ml for HPV-18 were seen. By comparison, GMTs for natural infection antibody levels were 30 (95% CI, 29-31) EU/ml in women who had cleared HPV-16 infection and 23 (95% CI, 22-24) EU/ml for HPV-18.

Among the target populations for an HPV-16/18 vaccine are early adolescent females before they engage in sexual activity. Because the above studies enrolled women 15-25 years of age, immunogenicity was subsequently evaluated in adolescent females 10-14 years of age (11). Among 10-14-year-olds (n=150) and 15-25-year-olds (n=403) who were seronegative at entry and who received three doses of vaccine, the GMT was higher for both antigens in the group aged 10-14 years (HPV-16 GMT: 17,273 EU/ml; HPV-18 GMT: 6864 EU/ml) than in the group aged 15-25 years (HPV-16 GMT: 7295 EU/ml; HPV-18 GMT: 3329 EU/ml).

In the phase III study, over 3,000 women in the vaccine and placebo groups participated in a safety assessment using diary cards to report symptoms experienced during the first 7 days after vaccination and symptoms within the first 30 days. Reports of serious adverse events among the entire cohort of over 18,000 women were also collected. Ninety percent of women in the vaccine group reported injection-site pain, but only 16% reported the highest grade of pain. Injection-site redness and swelling were reported by approximately 40% of the women. Local symptoms were more frequent in the vaccine group than the control group. However, most local symptoms were transient, with the mean duration of symptoms ranging from 2 to 3 days. Serious adverse events were reported by 3.5% of women in both the vaccine and control groups; however, in only 0.1% of the women in each group was the event judged to be vaccine-related. There were no differences between the vaccine group and the control group in new-onset autoimmune disease, new-onset chronic disease or abnormal pregnancy outcomes. Among 158 adolescent females aged 10-14 years, the vaccine safety profile was similar to that observed in the phase II study, and generally fewer symptoms were reported in this group than in women aged 15-25 years.

Conclusions

Cervarix™ has been shown to be safe and well tolerated, although published data for the large international phase III study are limited to the first year after vaccination. A three-dose regimen of the vaccine induces a robust serum antibody response, with titers maintained well above levels observed after natural infection for up to 5.5 years post-vaccination. The three-dose regimen is highly effective in preventing HPV-16/18 infections and related cervical disease. The interim analysis of the large international phase III study indicates that efficacy for preventing HPV-16/18-related cervical disease may be as high as 100%. Cervarix™ also provides significant cross-protec-

tion against infection with HPV-31 and -45, but the vaccine has not yet been shown to protect against cervical disease associated with these types. Continued follow-up of women participating in phase III trials should provide estimates of the longer term efficacy of the vaccine.

The vaccine has been introduced in Australia and approved for launch in the E.U., and a regulatory filing has been submitted in Japan.

Source

GlaxoSmithKline Biologicals (GB).

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