
EFFICACY OF A QUADRIVALENT HPV (TYPES 6, 11, 16, 18) L1 VLP VACCINE (GARDASIL®) AGAINST CERVICAL INTRAEPITHELIAL NEOPLASIA GRADES 1-3 AND EXTERNAL GENITAL DISEASE: A COMBINED ANALYSIS

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1. Objective and Methods: In addition to being the causative agent of cervical cancer, HPV may also lead to vulvar and vaginal cancer and their precursor lesions, as well as genital warts (GW). HPV types 6, 11, 16 and 18 cause ~70% of anogenital cancers/high-grade pre-cancers, 35-50% of low-grade dysplastic lesions, and >90% of GW. We present a combined analysis of 3 randomized, placebo-controlled trials to examine the impact of a quadrivalent vaccine on HPV 6, 11, 16 and 18-related external genital disease, including GW and cervical, vulvar and vaginal neoplasias of any grade (CIN 1-3, VIN 1-3 and VaIN 1-3). Immunogenicity and safety data will be also presented.

2. Results: 18,150 women (16-26 yrs) from the Americas, Europe and Asia were enrolled in 1 of 3 trials. Subjects were randomized to either quadrivalent vaccine or placebo. Vaccination occurred at day 1, and months 2 and 6. Genital tract specimens were obtained at day 1 and at 6-12 month intervals thereafter for a maximum of 48 months. Colposcopy referral was algorithm-based. Biopsies were HPV-typed.

2.1. Cervical lesions: Primary endpoints were HPV 6, 11, 16, 18-related cervical intraepithelial neoplasia (CIN 1-3), adenocarcinoma *in situ* (AIS), and cervical cancer. To be included in the analysis, subjects must have received ≥ 1 dose and be HPV 6, 11, 16, or 18 negative at day 1 by serology and DNA. Protocol violators were not excluded. Follow-up for case ascertainment started 30 days after the day 1 visit

The table below displays results. In these studies, no cases of cervical cancer were observed.

Conclusion: In this combined MITT analysis, prophylactic administration of a quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine (GARDASIL®) was highly efficacious in preventing HPV 6, 11, 16 and 18-related cervical neoplasias, including CIN 2/3 and AIS. If vaccine efficacy remains durable over time, these data suggest that implementation of mass immunization programs targeting adolescents should

result in a dramatic decrease in vaccine-HPV-type-related cervical disease, including cervical cancer caused by these types.

	Vaccine			Placebo			Efficacy (%)	95% CI
	n	Cases	Rate [†]	n	Cases	Rate [†]		
MITT								
By Lesion								
CIN 1	8625	8	<0.1	8673	106	0.6	92	(85-97)
CIN 2	8625	1	<0.1	8673	51	0.3	98	(89-100)
CIN 3 or AIS	8625	0	0	8673	44	0.3	100	(91-100)
[†] Cases/Subject years at risk*100								

2.2. External genital lesions

The endpoints were HPV 6, 11, 16, 18-related GW, CIN 1-3, VIN 1-3, VaIN 1-3 and cervical, vaginal or vulvar cancer. Analyses were done per protocol (PP) (subjects received 3 doses, had no major protocol violations, were HPV 6, 11, 16, or 18 seronegative at Day 1 and HPV 6, 11, 16 or 18 DNA negative Day 1 through month 7) and modified intention to treat (MITT) (subjects received ≥ 1 dose and were HPV 6, 11, 16, or 18 negative at day 1 by serology and DNA). Endpoint counts began after Month 7 and Day 30 in the PP and MITT analyses, respectively.

In the PP population, among 7897 vaccine and 7899 placebo recipients, the vaccine was 99% effective (95% CI: 95-100) in preventing HPV 6, 11, 16 or 18- related GW and vulvar/vaginal intraepithelial neoplasia of any grade. In this population, within an average of 17 months of follow-up, 113 histologically confirmed cases of the composite endpoint were observed in the placebo arm. There was one case of HPV 6-related condyloma in the vaccine group. A total of 8760 vaccine and 8786 placebo recipients were eligible for the MITT analysis. In this MITT population, the vaccine was 95% effective (95% CI: 90-98) for the primary endpoints. In these studies, there were no observed cases of vulvar or vaginal cancer related to vaccine HPV types.

Conclusion: In this combined analysis, prophylactic quadrivalent HPV vaccination with GARDASIL® was highly effective in preventing HPV 6, 11, 16 and 18-related GW and vulvar/vaginal pre-cancerous lesions through almost 2 years of follow-up. This intervention is expected to significantly reduce the burden of clinical diseases caused by HPV.

IMMUNOGENICITY

The vaccine GARDASIL® was highly immunogenic in adults and children with near 100% seroconversion rates. The anti-HPV responses are higher in adolescents than in adults, and decline post dose 3 and then reach a plateau that remains for at least 5 years.

SAFETY

The vaccine was well tolerated in individuals 9-26 years old who are negative or positive to 1 or more vaccine HPV type. Adverse experiences associated to injection site were slightly more common among vaccine recipients than among those receiving placebo.