PS10 Late breaking

Prophylactic use of quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine reduces cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma *in situ* (AIS) risk

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Background: CIN 2/3 and AIS are the obligate precursor lesions for cervical squamous cell- and adenocarcinoma, respectively. Thus, if prophylactic HPV vaccines are demonstrated to reduce the incidence of these precursor lesions, it can be inferred that the vaccines reduce risk of development of cervical cancer. A clinical program consisting of 4 randomized clinical trials was developed to evaluate the impact of a prophylactic HPV vaccine on the rates of these diseases. It is part of a program to assess the vaccine's impact on cervical cancer, CIN 1–3, and genital warts.

Methods: 20,541 women (16–26 yrs) from the Americas, Europe and Asia were enrolled in one of four trials. In one trial, subjects were randomized to either a monovalent HPV 16 L1 VLP vaccine or placebo. In 3 trials, subjects were randomized to either quadrivalent HPV (Types 6/11/16/18) L1 VLP vaccine or placebo. For all trials, vaccination occurred at day 1, and months 2 and 6. Genital tract specimens for Pap and HPV DNA tests were obtained at day 1 and at 6–12 months intervals thereafter for a maximum of 48 months. Colposcopy referral was algorithm-based. Biopsies were HPV-typed. Cytology, histology, and HPV detection were conducted centrally. A combined analysis of the 4 studies was prespecified in 2001. The primary endpoint was the combined incidence of HPV 16/18-related CIN 2/3, AIS, or cancer as read by a blinded pathology panel. In the HPV 16 vaccine study, only HPV 16-related cases were considered. Analyses were done in a per protocol (PP) population (subjects received 3 doses, had no major protocol violations, were HPV 16/18 seronegative at Day 1 and HPV 16/18 DNA negative Day 1 through month 7) and in a modified intention to treat (MITT) population (subjects received $\geqslant$1 dose and were HPV 16/18 negative at day 1). Endpoint counts began at Month 7 and Day 30 in the PP and MITT analyses, respectively.

Results: The table displays results. Vaccination was generally well tolerated.

	Vaccine		Placebo		Efficacy (%)	95%CI
	Cases[a]	Rate[b]	Cases[a]	Rate[b]		
PP (n=8487)						
CIN 2/3+	0	0	53	0.4	100	93–100*
CIN 2	0	0	36	0.3	100	89–100
CIN 3/AIS	0	0	32	0.2	100	88–100
MITT (n=9342)						
CIN 2/3+	1	<0.1	81	0.4	99	93–100*
CIN 2	1	<0.1	55	0.3	98	89–100
CIN 3/AIS	0	0	52	0.3	100	93–100

[a]Subjects counted once in each applicable category.
[b]Rate = n/Subject years at risk*100.
*P < 0.001

Conclusion: In this combined analysis, prophylactic quadrivalent HPV vaccination prevented HPV 16/18-related CIN 2/3 and AIS. This intervention is expected to greatly reduce the risk of cervical cancer.