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RESEARCH PAPER

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Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia and cervical infection in young Japanese women

Open follow-up of a randomized clinical trial up to 4 years post-vaccination

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Keywords: human papillomavirus, HPV-16/18 AS04-adjuvanted vaccine, efficacy, safety, Japan, cervical cancer

Abbreviations: AE, adverse event; ASC-US, atypical squamous cells of undetermined significance; ATP, according-to-protocol; ATP-E, according-to-protocol cohort for efficacy; ATP-I, according-to-protocol cohort for immunogenicity; CI, confidence interval; CIN, cervical intraepithelial neoplasia; DEIA, DNA enzyme immunoassay; DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; EL.U, ELISA units; GMT, geometric mean titre; HPV, human papillomavirus; LiPA, line probe assay; PATRICIA, PApilloma TRIal against Cancer In young Adults; PCR, polymerase chain reaction; SAE, serious adverse event; TVC, total vaccinated cohort; VE, vaccine efficacy.

In this open, extended follow-up study (NCT00929526, Clinicaltrials.gov), we evaluated the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine efficacy, immunogenicity and safety up to 4 years after first vaccination in Japanese women aged 20–25 years. In the initial randomized, double-blind study (NCT00316693), 1040 women received the study vaccine or hepatitis A control vaccine; 752 women were included in the follow-up study. In women from the according-to-protocol efficacy cohort (ATP-E), who were initially seronegative for the HPV type analyzed, no cervical intraepithelial neoplasia (CIN) grade 1 or greater (CIN1+) cases associated with HPV-16/18 were reported in the HPV group, while in the control group, 5 cases were identified in extended follow-up analyses (vaccine efficacy [VE] 100% [95% CI: −3.7–100]) and 8 cases in combined initial and follow-up studies analyses (VE 100% [42.2–100]). In the ATP-E, VE against CIN1+ and CIN2+ associated with high-risk HPV types reached 66.4% (21.6–87.1) and 83.0% (22.1–98.2) in extended follow-up analyses, and 63.4% (28.8–82.3) and 77.3% (30.4–94.4) in analyses of combined studies, respectively. During the 4-year period, protection against CIN1+ and CIN2+, irrespective of the HPV type, was 56.7% (32.8–72.6) and 54.9% (20.5–75.3) in women receiving ≥1 vaccine dose, regardless of baseline serostatus (total vaccinated cohort [TVC]) and 61.0% (11.8–84.2) and 73.9% (1.1–95.3) in women naïve to HPV infection at baseline (TVC-naïve), respectively. The high VE observed in Japanese women, accompanied by a sustained immune response and a clinically acceptable safety profile, support findings of large, international trials.

Introduction

In terms of incidence rates, cervical cancer is the third most common cancer in women worldwide and the eighth most common cancer in Japanese women, ranking second for women aged 15–44 y.[1,2] According to 2008 estimates, in a population of 56.69 million women aged 15 y and over in Japan, 8894 women are diagnosed with cervical cancer and 3350 die from the disease

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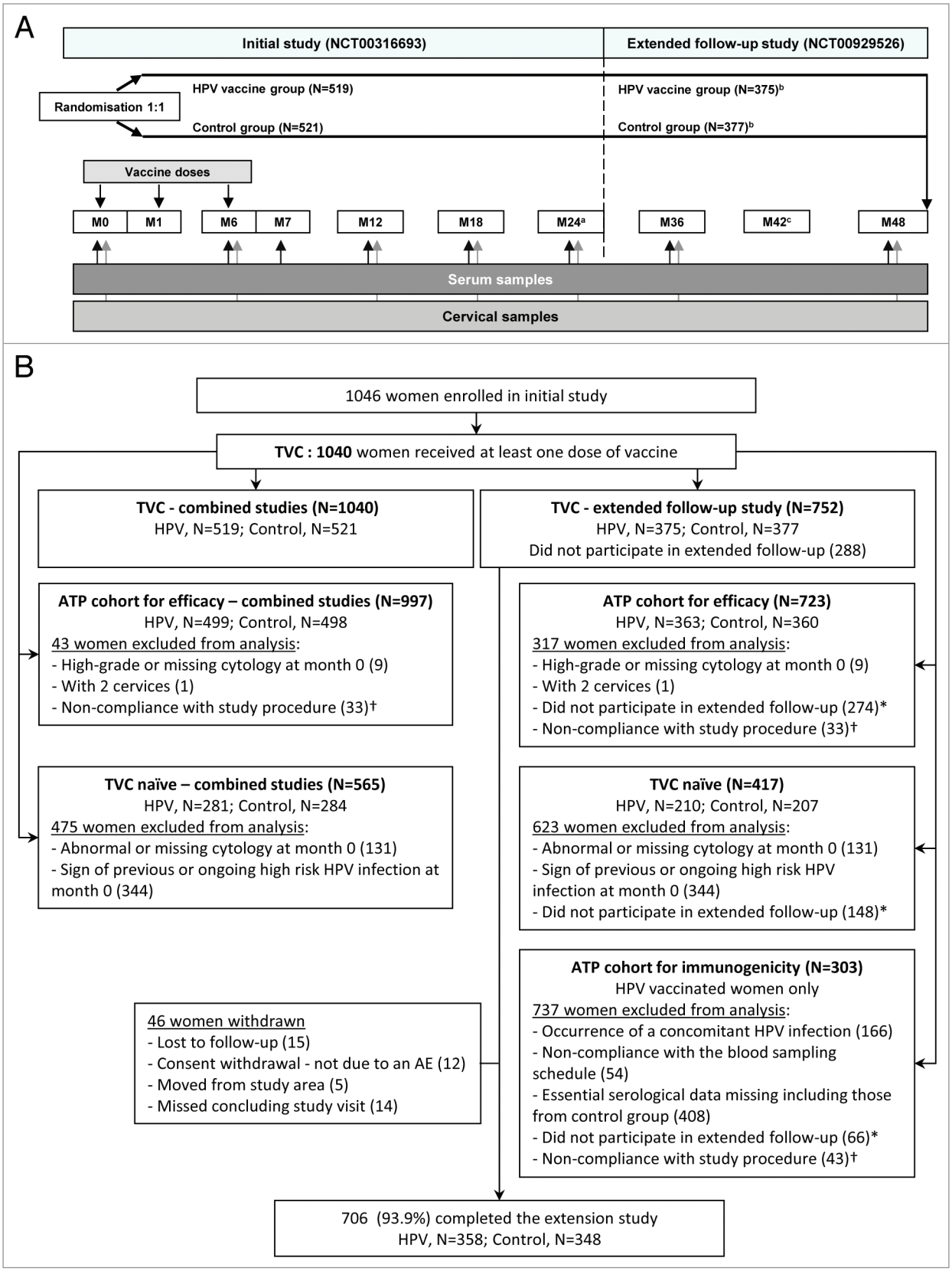

Figure 1. For figure legend see page 1782.

Figure 1. Study design (**A**) and flow of participants (**B**) throughout the study. [a]Women who received ≥1 dose of HPV-16/18 vaccine were invited for follow-up at month 24. [b]No women with high-grade cytology or missing cytology at baseline. [c]Additional cytopathological examination could be performed per cytology management algorithm at month 42 if required. *Number of women eliminated from the analysis of the concerned cohort under the reason of "not participated in extended follow-up." The other women who did not participate in the extended follow-up study were eliminated with other reasons indicated in the same box. †Non-compliance with study procedure includes protocol violation, or randomization code broken, or non-compliance with the vaccine dose/schedule in the initial study, or administration of vaccine(s)/medication(s) forbidden by the protocol. Abbreviations: ATP, according-to-protocol; HPV, HPV vaccine group; TVC, total vaccinated cohort; N, number of women; AE, adverse event.

every year.[2] Infection with human papillomavirus (HPV) has been identified as a major and necessary cause of cervical cancer.[3] At least 14 HPV genotypes are considered oncogenic, of which 2 major types, HPV-16 and -18, are responsible for up to 71% of cervical cancer cases worldwide.[4–7] The prevalence of oncogenic HPV types in cervical cancer does not seem to show significant geographical variation, although their relative importance may differ between regions.[4,6] Between 1999 and 2007, the most common HPV types in Japanese women with invasive cervical cancers were, in order of decreasing prevalence, HPV-16 (40.5%), HPV-18 (24.4%), HPV-52 (8.4%), HPV-58 (3.1%), and HPV-33 (3.1%).[8]

Well-organized screening programmes for sexually active women have proved an effective means of reducing morbidity and mortality associated with cervical cancer. However, these programmes have been mostly limited to countries, or regions, with the necessary level of infrastructure and availability of resources.[9] In Japan, low screening coverage has been attributed partly to poor knowledge and education about cervical cancer and screening.[10] Vaccination against HPV oncogenic types offers a complementary method to help prevent cervical cancer and associated pre-cancerous lesions related to HPV infection. Currently, vaccination against HPV is recommended in over 100 different countries, where 2 HPV vaccines are widely available: the HPV-16/18 AS04-adjuvanted vaccine (*Cervarix*®, GlaxoSmithKline Vaccines) and the HPV-6/11/16/18 aluminum-adjuvanted vaccine (*Gardasil*®, Merck). Both vaccines are immunogenic and show clinically acceptable safety profiles.[11–15] A number of large efficacy studies have shown sustained efficacy of these vaccines in the prevention of various cervical infection- and disease-related endpoints. In particular, efficacy data are available for up to 9.4 y following vaccination with the HPV-16/18 AS04-adjuvanted vaccine.[16–21] Data from a large global efficacy trial conducted in 14 different countries, the PApilloma TRIal against Cancer In young Adults (PATRICIA), showed high overall efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical intraepithelial neoplasia (CIN) grade 3 or greater (CIN3+), high efficacy against cervical infection with HPV-16/18 and their associated cytological and histological outcomes, and cross-protective efficacy against cervical infection and pre-cancer lesions caused by other types including HPV-31, -33, -45, and -51 up to 4 y post-vaccination.[22–25]

In Japan, the HPV-16/18 AS04-adjuvanted vaccine was approved on 16 October 2009 and was funded by the Ministry of Health, Labour and Welfare until April 2013 under a provisional priority immunisation program. In April 2013, HPV vaccination, targeting young girls before sexual exposure, was introduced into the routine immunisation schedule for adolescent girls aged 12–16 y, and universal mass vaccination was immediately implemented. A survey conducted in 2011 reported that 4.8% of Japanese girls had first sexual intercourse during their junior high school years (13- to 15-y-olds) and 23.6% of Japanese girls during their latter high school years (16- to 18-y-olds).[26] In a previous randomized, double-blind, controlled study (NCT00316693) conducted in young Japanese women aged 20–25 y, we demonstrated the efficacy of the HPV-16/18 AS04-adjuvanted vaccine against persistent infection with HPV-16 and -18 (6-mo as well as 12-mo definitions) during 2 y following the first vaccination.[27,28] Additionally, the vaccine has been shown to provide significant protection against persistent infection associated with a combination of 14 oncogenic HPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68).[27] Persistent infection with the same high-risk HPV type is considered as a predictor for moderate or high-grade cervical dysplasia and cancer.

The primary objective of this extended follow-up study, conducted up to 4 y after the first vaccination, was to evaluate the efficacy of the HPV-16/18 AS04-adjuvanted vaccine against CIN1+ lesions associated with HPV-16/18 during the follow-up period in healthy women who were, for the corresponding HPV type, seronegative before vaccination (month 0) and negative for HPV deoxyribonucleic acid (DNA) at months 0 and 6 in the initial study. The secondary objectives included the evaluation of the vaccine efficacy (VE) against CIN1+ lesions associated with HPV-16/18 for the combined analysis of initial and follow-up studies in women who were, for the corresponding HPV type, seronegative at month 0 and HPV DNA negative at months 0 and 6 in the initial study. Secondary objectives also included the evaluation of the VE against incident infection, 12-mo persistent infection and cytological abnormalities associated with HPV-16/18 during the follow-up period and for the combined analysis of initial and follow-up studies in women who were, for the corresponding HPV type, seronegative at month 0 and HPV DNA negative at months 0 and 6 in the initial study; the VE against incident infection, 12-mo persistent infection, cytological abnormalities and CIN1+ lesions associated with high-risk HPV types during the follow-up period and for the combined analysis of initial and follow-up studies in women who were, for the corresponding HPV type, HPV DNA negative at months 0 and 6 in the initial study; the persistence of the humoral anti-HPV-16 and -18 immune responses during 4 y after the first vaccination; and the assessment of the safety and pregnancy outcomes over the total follow-up period. To further explore the potential public health effect of the HPV-16/18 AS04-adjuvanted vaccine, its overall efficacy in preventing CIN1+, CIN2+, and CIN3+, irrespective of the HPV type associated with the lesion, was evaluated in women regardless of their baseline HPV infection or cytology status (total vaccinated cohort [TVC]) and in women with no evidence of previous HPV infection at baseline (TVC-naïve cohort, approximating girls before sexual debut).

Table 1. Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with HPV-16/18 in women from the ATP-E (**A**) who were initially seronegative and (**B**) regardless of their baseline serostatus

	Extended follow-up							Combined study period						
	HPV vaccine[a]			Control[a]			Efficacy (95% CI)	HPV vaccine[a]			Control[a]			Efficacy (95% CI)
	N	Cases	Rate	N	Cases	Rate		N	Cases	Rate	N	Cases	Rate	
(A) Seronegative[b]														
Incident infection														
HPV-16/18	332	7	2.65	335	28	11.75	77.4% (47.1–91.7)	406	12	1.01	403	58	5.27	80.8% (63.9–90.6)
HPV-16	286	3	1.28	289	16	7.71	83.4% (41.9–96.9)	349	7	0.68	350	33	3.37	79.8% (53.5–92.4)
HPV-18	294	5	2.13	291	13	6.06	64.8% (–5.3–90.2)	357	8	0.76	353	28	2.81	73.1% (39.4–89.4)
Persistent infection[c]														
HPV-16/18	257	0	0.00	241	9	4.10	100% (54.3–100)	382	0	0.00	383	16	1.39	100% (74.8–100)
HPV-16	225	0	0.00	206	6	3.18	100% (25.0–100)	329	0	0.00	331	12	1.21	100% (65.0–100)
HPV-18	227	0	0.00	209	4	2.07	100% (–36.2–100)	338	0	0.00	335	5	0.49	100% (–5.8–100)
ASC-US+														
HPV-16/18	332	3	1.12	335	11	4.39	74.4% (3.2–95.4)	406	4	0.33	403	20	1.72	80.6% (41.9–95.2)
HPV-16	286	2	0.85	289	10	4.69	81.9% (14.9–98.1)	349	2	0.19	350	16	1.59	87.8% (48.3–98.6)
HPV-18	294	1	0.42	291	2	0.90	53.5% (–793.8–99.2)	357	2	0.19	353	5	0.48	61.1% (–137.6–96.3)
CIN1+														
HPV-16/18	332	0	0.00	335	5	1.92	100% (–3.7–100)	406	0	0.00	404	8	0.67	100% (42.2–100)
HPV-16	286	0	0.00	289	5	2.26	100% (–0.4–100)	349	0	0.00	350	7	0.68	100% (31.5–100)
HPV-18	294	0	0.00	291	0	0.00	-	357	0	0.00	354	1	0.10	100% (–3708.2–100)
CIN2+														
HPV-16/18	332	0	0.00	335	4	1.54	100% (–44.0–100)	406	0	0.00	404	5	0.42	100% (–8.0–100)
HPV-16	286	0	0.00	289	4	1.81	100% (–39.4–100)	349	0	0.00	350	5	0.49	100% (–7.8–100)
HPV-18	294	0	0.00	291	0	0.00	-	357	0	0.00	354	0	0.00	-

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine) or the Hepatitis A vaccine (Control); [b]Women were HPV DNA negative at months 0 and 6 and seronegative at baseline for the corresponding HPV types; [c]12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; N, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least on event per year (per 100 women) (cases/follow-up period in years). Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

Table 1. Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with HPV-16/18 in women from the ATP-E (**A**) who were initially seronegative and (**B**) regardless of their baseline serostatus (continued)

	Extended follow-up							Combined study period						
	HPV vaccine[a]			Control[a]			Efficacy (95% CI)	HPV vaccine[a]			Control[a]			Efficacy (95% CI)
	N	Cases	Rate	N	Cases	Rate		N	Cases	Rate	N	Cases	Rate	
(B) Regardless of baseline serostatus														
Incident infection														
HPV-16/18	358	7	2.48	355	32	12.66	80.4% (54.7–92.7)	438	14	1.10	429	63	5.40	79.6% (63.3–89.5)
HPV-16	343	3	1.09	327	18	7.62	85.7% (50.8–97.3)	417	8	0.65	395	35	3.15	79.3% (54.6–91.7)
HPV-18	348	5	1.81	332	15	6.04	70.1% (13.4–91.5)	426	9	0.72	404	32	2.80	74.4% (45.0–89.2)
Persistent infection[c]														
HPV-16/18	276	0	0.00	259	11	4.69	100% (64.2–100)	413	0	0.00	409	19	1.56	100% (79.5–100)
HPV-16	266	0	0.00	236	7	3.24	100% (40.4–100)	394	0	0.00	375	14	1.24	100% (72.2–100)
HPV-18	270	0	0.00	242	5	2.23	100% (4.1–100)	402	0	0.00	385	6	0.51	100% (20.3–100)
ASC-US+														
HPV-16/18	358	3	1.05	355	13	4.88	78.5% (21.7–96.1)	438	4	0.31	429	21	1.70	81.7% (45.8–95.4)
HPV-16	343	2	0.73	327	11	4.53	84% (26.6–98.3)	417	2	0.16	395	17	1.49	89.2% (54.3–98.8)
HPV-18	348	1	0.36	332	3	1.17	69.6% (-278.1–99.4)	426	2	0.16	404	6	0.51	68.7% (–75.1–96.9)
CIN1+														
HPV-16/18	358	0	0.00	355	7	2.52	100% (34.1–100)	438	0	0.00	431	10	0.79	100% (56.6–100)
HPV-16	343	0	0.00	327	6	2.38	100% (24.0–100)	417	0	0.00	397	8	0.69	100% (45.2–100)
HPV-18	348	0	0.00	332	1	0.38	100% (-3479.8–100)	426	0	0.00	406	2	0.17	100% (–402.6–100)
CIN2+														
HPV-16/18	358	0	0.00	355	6	2.16	100% (19.4–100)	438	0	0.00	431	7	0.55	100% (32.3–100)
HPV-16	343	0	0.00	327	5	1.98	100% (2.3–100)	417	0	0.00	397	6	0.52	100% (20.5–100)
HPV-18	348	0	0.00	332	1	0.38	100% (-3479.8–100)	426	0	0.00	406	1	0.08	100% (-3587.9–100)

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine) or the Hepatitis A vaccine (Control); [b]Women were HPV DNA negative at months 0 and 6 and seronegative at baseline for the corresponding HPV types; [c]12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; N, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least on event per year (per 100 women) (cases/follow-up period in years). Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

Table 2. Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with high-risk HPV types in women from the ATP-E, regardless of their baseline serostatus

	Extended follow-up							Combined study period						
	HPV vaccine[a]			Control[a]				HPV vaccine[a]			Control[a]			
	N	Cases	Rate	N	Cases	Rate	Efficacy (95% CI)	N	Cases	Rate	N	Cases	Rate	Efficacy (95% CI)
Incident infection														
HPV-31/33/45	363	12	4.18	359	13	4.84	13.6% (-105.4–64.0)	444	16	1.24	433	22	1.76	29.4% (−40.7–65.4)
HPV-31/33/45/52/58	363	53	19.86	359	44	17.43	-14.0% (−74.1–25.0)	444	79	6.57	433	82	7.05	6.8% (-28.6–32.4)
any non-vaccine high-risk type	363	83	33.46	359	86	37.79	11.4% (-21.2–35.3)	444	137	12.55	433	151	14.59	14.0% (−9.1–32.3)
any high-risk type	363	87	35.23	359	98	45.27	22.2% (−5.0–42.4)	444	145	13.53	433	175	17.88	24.4% (5.2–39.7)
Persistent infection[b]														
HPV-31/33/45	280	0	0.00	261	3	1.23	100% (-122.3–100)	419	3	0.23	413	4	0.32	26.9% (-332.0–89.3)
HPV-31/33/45/52/58	280	8	3.10	261	11	4.66	33.5% (−81.7–76.8)	419	17	1.34	413	17	1.38	2.4% (-103.4–53.2)
any non-vaccine high-risk type	280	19	7.68	261	23	10.23	25.0% (−44.0–61.4)	419	34	2.75	413	40	3.35	18.0% (-32.9–49.7)
any high-risk type	280	19	7.68	261	31	14.25	46.1% (1.6–71.3)	419	34	2.75	413	53	4.54	39.4% (5.0–61.8)
ASC-US+														
HPV-31/33/45	363	2	0.69	359	4	1.45	52.6% (−231.1–95.7)	444	5	0.38	433	6	0.47	18.5% (-220.5–80.3)
HPV-31/33/45/52/58	363	14	4.92	359	21	7.91	37.8% (-28.4–70.7)	444	23	1.79	433	35	2.83	36.5% (-10.5–64.2)
any non-vaccine high-risk type	363	31	11.13	359	40	15.72	29.2% (-16.1–57.2)	444	51	4.07	433	61	5.08	19.9% (-18.2–45.9)
any high-risk type	363	33	11.89	359	45	17.92	33.6% (−6.3–59.0)	444	54	4.32	433	70	5.89	26.7% (−6.1–49.6)
CIN1+														
HPV-31/33/45	363	0	0.00	359	2	0.71	100% (−403.9–100)	444	0	0.00	435	3	0.23	100% (-135.9–100)
HPV-31/33/45/52/58	363	5	1.69	359	10	3.59	52.9% (−51.4–87.4)	444	9	0.69	435	18	1.42	51.7% (-13.3–80.9)
any non-vaccine high-risk type	363	8	2.71	359	18	6.57	58.7% (0.3–84.5)	444	13	1.00	435	28	2.23	55.4% (10.9–78.8)
any high-risk type	363	8	2.71	359	22	8.05	66.4% (21.6–87.1)	444	13	1.00	435	34	2.72	63.4% (28.8–82.3)

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; any high-risk type = high-risk oncogenic HPV types, i.e., HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; any non-vaccine high-risk type = 12 non-vaccine high-risk oncogenic HPV types, i.e., HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine) or the Hepatitis A vaccine (Control); [b]12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; N, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least one event per year (per 100 women) (cases/follow-up period in years); Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

Table 2. Incidence rates and vaccine efficacy against viral infection, cytological, and histological endpoints associated with high-risk HPV types in women from the ATP-E, regardless of their baseline serostatus (continued)

	Extended follow-up							Combined study period						
	HPV vaccine[a]			Control[a]				HPV vaccine[a]			Control[a]			
	N	Cases	Rate	N	Cases	Rate	Efficacy (95% CI)	N	Cases	Rate	N	Cases	Rate	Efficacy (95% CI)
CIN2+														
HPV-31/33/45	363	0	0.00	359	1	0.36	100% (-3591.1–100)	444	0	0.00	435	1	0.08	100 (–3704.8–100)
HPV-31/33/45/52/58	363	1	0.34	359	5	1.79	81.1% (–68.6–99.6)	444	2	0.15	435	8	0.63	75.7% (-21.6–97.5)
any non-vaccine high-risk type	363	2	0.68	359	7	2.52	73.2% (–40.8–97.3)	444	4	0.30	435	12	0.94	67.7% (–6.6–92.4)
any high-risk type	363	2	0.68	359	11	3.97	83.0% (22.1–98.2)	444	4	0.30	435	17	1.34	77.3% (30.4–94.4)

The left part is based on case counting during the extended follow-up period only; the right part shows data for the combined (initial plus extended) study period; any high-risk type = high-risk oncogenic HPV types, i.e., HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; any non-vaccine high-risk type = 12 non-vaccine high-risk oncogenic HPV types, i.e., HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine) or the Hepatitis A vaccine (Control); [b]12-mo definition: women with at least 2 consecutive samples positive for the same HPV type over a minimum of 10 mo; N, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least one event per year (per 100 women) (cases/follow-up period in years); Abbreviations: ASC-US+, atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions; CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; 95% CI, 95% confidence interval (lower limit–upper limit).

Results

Figure 1A shows the overall study design, including the initial and the extended follow-up studies, and **Figure 1B**, the disposition of the participants in the analyzed cohorts of the extended follow-up study, and combined initial and follow-up studies. In the extended follow-up study, 752 eligible women attended at least one visit and were included in the TVC: 375 women in the HPV vaccine group received at least one dose of the HPV-16/18 AS04-adjuvanted vaccine and 377 women in the control group received at least one dose of the hepatitis A control vaccine (*Aimmugen*™, Kaketsuken). Of these, 723 (96.1%) women were included in the according-to-protocol (ATP) cohort for efficacy (ATP-E), 417 (55.5%) women in the TVC-naïve, and 303 (40.3%) in the ATP cohort for immunogenicity (ATP-I). For combined analyses of initial and follow-up studies, the TVC included all 1040 vaccinated women, of whom 997 (95.9%) women were included in the ATP-E and 565 (54.3%) women in the TVC-naïve. The number of women included in the different cohorts was similar between the HPV vaccine and control groups. The baseline characteristics with respect to the age, history of HPV infection and cervical cytology status were similar in the HPV vaccine and the control groups, as described previously (data not shown).[29,30]

Vaccine efficacy against clinical endpoints associated with HPV-16/18

The efficacy of the HPV-16/18 AS04-adjuvanted vaccine in preventing incident infection, 12-mo persistent infection, cytological abnormalities, and CIN1+ and CIN2+ lesions associated with HPV-16/18 is summarized in **Table 1** for women included in the ATP-E, who were either seronegative at baseline for the HPV type analyzed or regardless of their serostatus. Results of the additional analysis in the TVC-naïve are presented in **Table S1**.

In the primary analysis of VE against histological clinical endpoints associated with HPV-16/18, which was performed in women from the ATP-E who were seronegative at baseline for the HPV type analyzed, no cases of CIN1+ lesions were accrued in the HPV vaccine group during the extended follow-up period, while 5 CIN1+ cases were identified in the control group (100% VE, 95% confidence interval [CI] –3.7–100). Cumulatively, 8 CIN1+ cases were identified in the combined analysis of initial and follow-up studies, all in the control group (100% VE, 95% CI 42.2–100). Of these 8 cases, 5 were identified as CIN2+ (100% VE, 95% CI –8.0–100).

In women from the ATP-E, regardless of their baseline serostatus, CIN1+ lesions associated with HPV-16/18 remained undetectable in the HPV vaccine group, while in the control group, 7 CIN1+ cases were identified during the extended follow-up period (100% VE, 95% CI 34.1–100) and 10 CIN1+ cases in the combined analysis of initial and follow-up studies (100% VE, 95% CI 56.6–100). Of these 10 cases, 7 were identified as CIN2+ (100% VE, 95% CI 32.3–100).

High VE was also observed against cytological (atypical squamous cells of undetermined significance [ASC-US+]) and virological endpoints (incident infection and 12-mo persistent infection) associated with HPV-16/18 in the ATP-E for the follow-up and combined study analyses.

Vaccine efficacy against clinical endpoints associated with high-risk HPV types

The efficacy of the HPV-16/18 AS04-adjuvanted vaccine in preventing incident infection, 12-mo persistent infection,

Table 3. Incidence rates and overall vaccine efficacy against histological endpoints irrespective of the HPV type in the TVC and TVC-naïve over the combined 4-y study period

		HPV vaccine[a]			Control[a]			
Cohort	Endpoint	N	Cases	Rate	N	Cases	Rate	Efficacy (95% CI)
TVC	CIN1+	464	31	2.00	463	68	4.62	56.7% (32.8–72.6)
	CIN2+	464	19	1.22	463	41	2.69	54.9% (20.5–75.3)
	CIN3+	464	9	0.57	463	14	0.89	36.4% (−57.8–75.7)
TVC-naïve[b]	CIN1+	254	9	1.02	251	22	2.62	61.0% (11.8–84.2)
	CIN2+	254	3	0.34	251	11	1.30	73.9% (1.1–95.3)
	CIN3+	254	0	0.00	251	2	0.23	100% (−417.0–100)

Data shown are for the combined (initial plus extended) study period, with case counting starting the day after receipt of the first vaccine dose; [a]Women were originally vaccinated with either the HPV-16/18 AS04-adjuvanted vaccine (HPV) or the Hepatitis A vaccine (Control); [b]Women were HPV naïve at baseline, i.e., DNA negative at months 0 and 6 and seronegative at baseline and with normal cytology at baseline in the initial study; N, number of women included in each group; Cases, number of women reporting at least one event; Rate, incidence rate of women reporting at least one event per year (per 100 women) (cases/follow-up period in years). Abbreviations: CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; CIN3+, cervical intraepithelial neoplasia grade 3 or greater; TVC, total vaccinated cohort; 95% CI, 95% confidence interval (lower limit–upper limit).

cytological abnormalities, and CIN1+ and CIN2+ lesions associated with the 14 high-risk HPV types, with the 12 non-vaccine high-risk HPV types, and with 2 composites of most common non-vaccine high-risk HPV types (HPV-31/33/45 and HPV-31/33/45/52/58) is summarized in **Table 2** for the women included in the ATP-E regardless of their baseline serostatus. Results related to the additional analysis in the TVC-naïve are presented in **Table S2**.

In the ATP-E, CIN1+ cases associated with high-risk HPV types were identified in 8 women in the HPV vaccine group and 22 women in the control group during the extended follow-up period (66.4% VE, 95% CI 21.6–87.1), and in 13 women in the HPV vaccine group and 34 women in the control group in the combined analysis of initial and follow-up studies (63.4% VE, 95% CI 28.8–82.3). In the HPV vaccine group, none of the CIN1+ cases were associated with vaccine types HPV-16/18 or with 3 most prevalent non-vaccine high-risk HPV types HPV-31/33/45. VE in preventing CIN1+ lesions associated with 12 non-vaccine high-risk HPV types and with the composite of 5 common non-vaccine high-risk HPV types HPV-31/33/45/52/58 was above 50% in the analyses of both the extended follow-up period and the combined initial and follow-up periods. In the analysis of CIN1+ cases associated with HPV-31/33/45, no cases were identified in the HPV vaccine group, while in the control group, 2 CIN1+ cases were identified during the extended follow-up period (100% VE, 95% CI −403.9–100) and 3 CIN1+ cases in the combined analysis of initial and follow-up studies (100% VE, 95% CI -135.9–100). CIN2+ cases associated with high-risk HPV types were identified in 2 women in the HPV vaccine group and in 11 women in the control group during the extended follow-up period (83.0% VE, 95% CI 22.1–98.2), and in 4 women in the vaccine group and 17 women in the control group in the combined analysis of initial and follow-up studies (77.3% VE, 95% CI 30.4–94.4). CIN2+ cases associated with 12 non-vaccine high-risk HPV types were identified in 2 women in the HPV vaccine group and 7 women in the control group during the extended follow-up period (73.2% VE, 95% CI −40.8–97.3), and in 4 women in the vaccine group and 12 women in the control group in the combined analysis of initial and follow-up studies (67.7% VE, 95% CI −6.6–92.4). In the HPV group, 1 and 2 CIN2+ cases were associated with HPV-31/33/45/52/58 during the extended follow-up and in the combined study periods, respectively, while in the control group 5 and 8 CIN2+ cases were identified during the extended follow-up and in the combined study periods, respectively. In the HPV group no CIN2+ cases associated with HPV-31/33/45 were identified while 1 case was identified in the control group during the extended follow-up.

VE against cytological (ASC-US+) and virological endpoints (incident infection and 12-mo persistent infection) associated with the 14 high-risk HPV types, the 12 non-vaccine high-risk HPV types, and the 2 composites of common non-vaccine high-risk HPV types (HPV-31/33/45 and HPV-31/33/45/52/58) was also evaluated in the ATP-E and the TVC-naïve.

Overall efficacy against histological endpoints irrespective of the HPV type

Table 3 summarizes the efficacy of the HPV-16/18 AS04-adjuvanted vaccine against CIN1+, CIN2+, and CIN3+ irrespective of the HPV type identified in the lesions for the combined analysis of initial and follow-up studies in the TVC and the TVC-naïve. In the TVC, 99 cases of CIN1+ were identified: 31 in the HPV vaccine group and 68 in the control group, resulting in an overall VE against CIN1+ of 56.7%

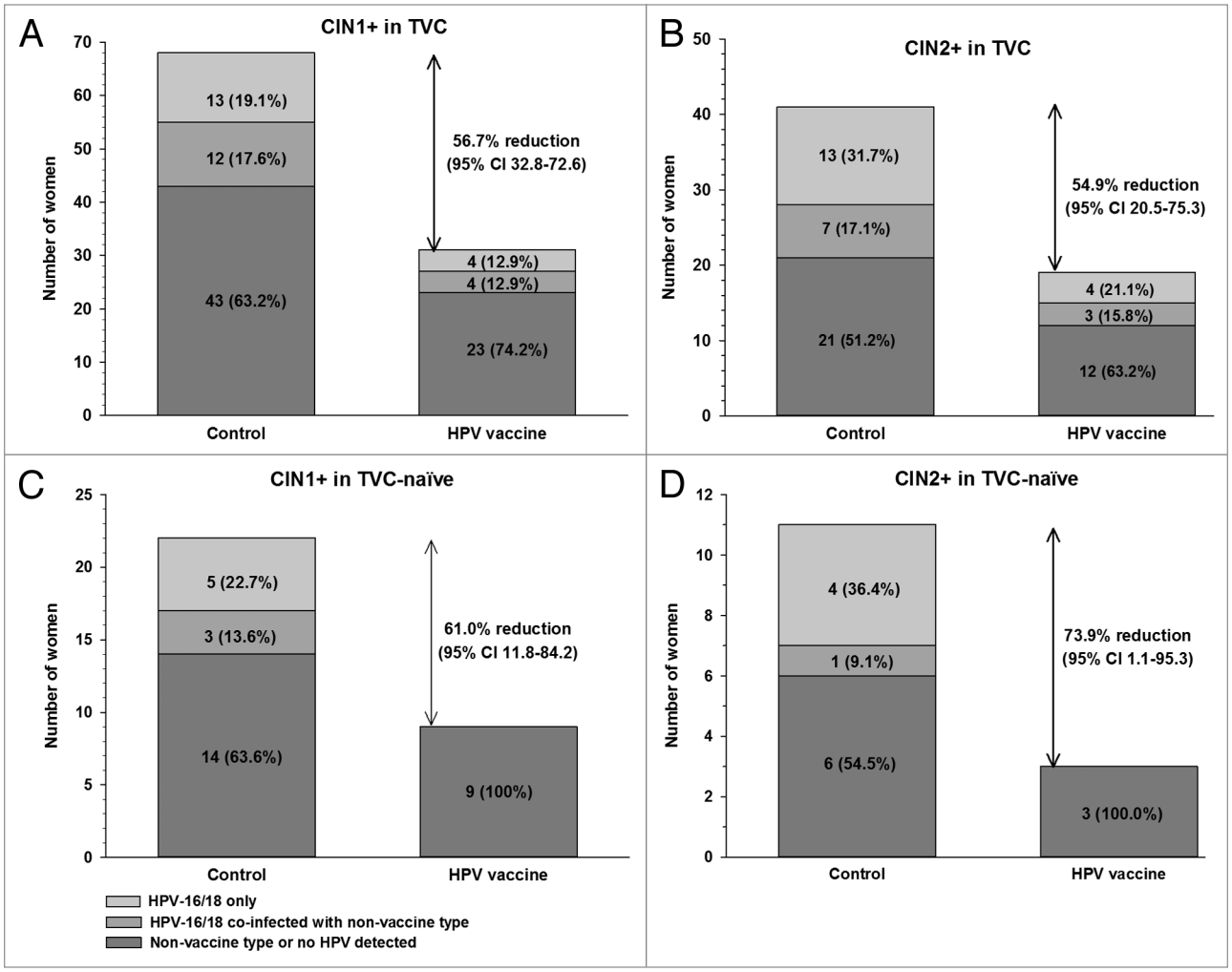

Figure 2. Number of cases of CIN1+ (**A and C**) and CIN2+ (**B and D**) associated with vaccine and non-vaccine HPV types in the TVC (**A and B**) and TVC-naïve (**C and D**) over the combined 4-y study period. Number of cases is shown inside the bars. Women included in the analysis of the TVC-naïve cohort were HPV DNA negative for all 14 oncogenic HPV types tested, seronegative for HPV-16 and HPV-18, and had negative cytology at baseline. Oncogenic HPV types tested were HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68. Follow-up period started on the day after the first vaccine dose. Abbreviations: CIN1+, cervical intraepithelial neoplasia grade 1 or greater; CIN2+, cervical intraepithelial neoplasia grade 2 or greater; TVC, total vaccinated cohort.

(95% CI 32.8–72.6). In the TVC-naïve, VE against CIN lesions irrespective of HPV type in the lesion was notably high; 9 CIN1+, 3 CIN2+, and no CIN3+ cases were observed in the HPV vaccine group compared with 22 CIN1+, 11 CIN2+, and 2 CIN3+ cases in the control group, representing 61.0% VE (95% CI 11.8–84.2) against CIN1+, 73.9% VE (95% CI 1.1–95.3) against CIN2+, and 100% VE (95% CI –417.0–100) against CIN3+.

In the TVC, 23 CIN1+ cases (74.2%) in the HPV vaccine group were associated with a non-vaccine type or no HPV DNA detected and 8 CIN1+ cases (25.8%) were associated with HPV-16/18 including 4 cases (12.9%) associated with HPV-16/18 only and 4 cases (12.9%) associated with co-infection of HPV-16/18 and a non-vaccine type (**Fig. 2A**). All those 8 CIN1+ cases associated with HPV-16/18 were found in women who were positive for HPV-16/18 DNA at baseline. In the control group, 43 CIN1+ cases (63.2%) were associated with a non-vaccine type or no HPV-DNA detected and 25 CIN1+ cases (36.8%) were associated with HPV-16/18 including 13 cases (19.1%) associated with HPV-16/18 only and 12 cases (17.6%) associated with co-infection of HPV-16/18 and a non-vaccine type. Fifteen out of 25 CIN1+ cases (60%) associated with HPV-16/18 were detected in women who were positive for HPV-16/18 DNA at baseline. In the HPV vaccine group, 19 CIN2+ cases were identified: 12 CIN2+ cases (63.2%) were associated with a non-vaccine type and 7 CIN2+ cases (36.8%) were associated with HPV-16/18 including 4 cases (21.1%) associated with HPV-16/18 only and 3 cases (15.8%) associated with co-infection of HPV-16/18 and a non-vaccine type (**Fig. 2B**). In the control group, 41 CIN2+ cases were identified: 21 CIN2+ cases (51.2%) were associated with a non-vaccine type and 20 CIN2+ cases (48.8%) were associated with HPV-16/18 including 13 cases (31.7%) associated with HPV-16/18 only and 7 cases (17.1%) associated with co-infection of HPV-16/18 and a non-vaccine type.

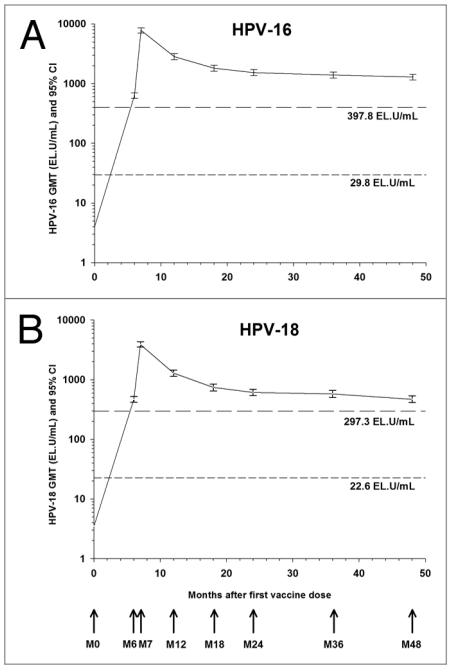

Figure 3. Anti-HPV-16 and anti-HPV-18 antibody GMTs from month 0 in initial study to month 48 in the present study (ATP kinetic cohort [N = 232 for HPV-16 and N = 233 for HPV-18]). The kinetics of the immune responses were evaluated in women from the ATP-I who were seronegative for the corresponding HPV type at baseline and had data available for each time point (ATP kinetic cohort). Long dashed lines: antibody titers at the plateau level (months 45–50) in a previous study in which sustained protection with the HPV-16/18 AS04-adjuvanted vaccine was shown up to 6.4 y post-vaccination (i.e., 397.8 [344.7–459.1] EL.U/mL for HPV-16 and 297.3 [258.2–342.2] EL.U/mL for HPV-18).[21] Short dashed lines: antibody titers in women (aged 15–25 y at time of enrolment) who were presumed to have cleared a natural infection prior to enrolment in a previous study (i.e., who were HPV DNA negative and seropositive at baseline for the HPV type analyzed; 29.8 [28.5–31.0] EL.U/mL for HPV-16 and 22.6 [21.6–23.6] EL.U/mL for HPV-18).[24] Abbreviations: 95% CI, 95% confidence interval (lower limit-upper limit); EL.U, ELISA units; GMT, geometric mean titer; M, month.

In the TVC naïve, no CIN1+ or CIN2+ cases associated with HPV-16/18 were observed in the HPV vaccine group (**Fig. 2C and D**). In the control group, 8 CIN1+ cases (36.4%) were associated with HPV-16/18, including 5 cases (22.7%) associated with HPV-16/18 only and 3 cases (13.6%) associated with co-infection of HPV-16/18 and a non-vaccine type (**Fig. 2C**). Five CIN2+ cases (45.5%) associated with HPV-16/18 were observed in the control group, including 4 cases (36.4%) associated with HPV-16/18 only and 1 case (9.1%) associated with co-infection of HPV-16/18 and a non-vaccine type (**Fig. 2D**).

Persistence of the anti-HPV-16 and -18 humoral immune responses

In the ATP-I, all women were seropositive for anti-HPV-16 and -18 antibodies at the end of the 48-mo follow-up. In women from the ATP-I who were seronegative at baseline, anti-HPV-16 and -18 geometric mean titers (GMTs, enzyme-linked immunosorbent assay [ELISA] units/mL) at month 48 were 1283.2 EL.U/mL (95% CI: 1150.1–1431.7) and 473.0 EL.U/mL (95% CI: 416.8–536.8). **Figure 3A and B** show the kinetics of the anti-HPV-16 and -18 antibody responses in women from the ATP kinetic cohort, which included 232 and 233 women in the HPV vaccine group for HPV-16 and -18, respectively. Following a peak response at month 7, GMTs for antibodies against HPV-16 and -18 showed a decline until about month 18, reaching a plateau phase thereafter. Anti-HPV-16 and -18 GMTs at month 48 remained at least 20-fold higher than antibody titers measured after naturally acquired infection in 15- to 25-y-old women in a previous study (NCT00122681)[24] and similar to the antibody titers at the plateau phase observed 45–50 mo after the vaccination in 15- to 25-y-old women in a previous study (NCT00120848), wherein vaccine efficacy against HPV-16/18 infection and associated cytological and histopathological lesions was demonstrated.[21]

Safety

During the combined initial and follow-up studies period, the proportion of women with serious adverse events (SAEs), new onset chronic diseases, new onset autoimmune diseases and medically significant conditions were similar between the HPV vaccine and the control groups. The numbers and rates of pregnancies and pregnancy outcomes were also similar between the groups (**Table S3**).

Discussion

Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against histological lesions associated with HPV-16/18 and other high-risk HPV types, and overall protection against histological lesions were evaluated for the first time in young Japanese women up to 4 y after the first vaccination. In the initial study, which was conducted prior to this extended follow-up, efficacy of the study vaccine against persistent infection with HPV-16 and HPV-18 (6-mo and 12-mo definitions) was demonstrated up to 2 y after the first vaccination in this population.[27]

In the evaluation of histological endpoints associated with HPV-16/18, we observed very high VE estimates in preventing CIN1+ and CIN2+ lesions, in line with the high efficacy of the HPV-16/18 AS04-adjuvanted vaccine against CIN1+, CIN2+, and CIN3+ lesions that was observed in a recently reported large efficacy study (PATRICIA) conducted in 14 different countries during a follow-up period of 4 y.[22] In the present study, we also observed a very high efficacy of the HPV-16/18 AS04-adjuvanted vaccine against 12-mo persistent infection with HPV-16/18. This is consistent with the 6-mo persistent infection results observed in the initial study,[27] and with previous observations of VE against persistent HPV-16/18 infection in similar age groups, which were reported for both 6-mo and 12-mo persistent infections in the large global trial PATRICIA[22] and for 12-mo persistent infections in a large efficacy trial in Costa Rica.[31] Persistent infection with oncogenic HPV types is considered to be a necessary cause of cervical cancer worldwide[3] and together with cervical pre-cancerous lesions serves as a surrogate marker for the risk of cervical cancer.[32,33] Other efficacy trials have demonstrated similarly high and sustained

efficacy of the HPV-16/18 AS04-adjuvanted vaccine against histological and viral infection endpoints associated with HPV-16/18 in women from Brazil, the United States of America, and Canada.[16–21] The longest follow-up study published to date shows efficacy data up to 9.4 y.[18]

Previous efficacy trials have shown cross-protection induced by the HPV-16/18 AS04-adjuvanted vaccine against HPV types 31, 33, 45, and 51,[17,23,25] and there are also reports of some cross-protection observed with the quadrivalent HPV-6/11/16/18 vaccine.[34] Although the present study was not powered to evaluate potential cross-protection against lesions and persistent infections associated with individual non-vaccine types, we were able to show high efficacy of the HPV-16/18 AS04-adjuvanted vaccine in preventing CIN1+ and CIN2+ lesions associated with 1 or more of the 14 high-risk HPV types, which is consistent with previous findings observed in the initial study.[27]

Although the ATP-E cohort was used for the primary analyses of this study, the TVC and TVC-naïve may be more clinically relevant. In particular, the TVC-naïve may more closely resemble the primary target population for HPV vaccination programs worldwide, corresponding to girls before sexual debut who are at a lower risk of having any previous or ongoing HPV infection. We therefore evaluated overall protection induced by the vaccine against histological endpoints, irrespective of the HPV type associated with the lesion in these cohorts. The high efficacy of the HPV-16/18 AS04-adjuvanted vaccine against CIN1+ and CIN2+, observed irrespective of the HPV type, in the TVC naïve and over the combined study period, suggests that this vaccine can offer high overall protection against CIN lesions in young Japanese women before sexual debut.

The efficacy of the HPV-16/18 AS04-adjuvanted vaccine seemed to be reached seemingly regardless of the geographical location, the circulating HPV types, the ethnicity of the population, and the methodology used, since our results were in line with larger trials of similar duration and vaccination age, such as the PATRICIA[22–25] and the Costa Rican trials.[31] Furthermore, the epidemiology of cervical cancer and of the most common associated HPV types has been shown to vary little between regions worldwide.[5,6]

Immunogenicity analyses revealed persistence of high antibody titers in women who received the HPV-16/18 AS04-adjuvanted vaccine up to 48 mo after the first vaccination, in-line with the plateau values reported for months 18–24 in the initial study.[27] Although there is currently no correlate of protection established for HPV-16/18 infection, other recent large efficacy trials can provide benchmarks for comparison. For instance, vaccination should induce higher antibody levels against HPV-16 and -18 than those measured in girls and young women (15–25 y) who were presumed to have cleared previous infection with these HPV types (29.8 [95%CI 28.5–31.0] EL.U/mL for HPV-16; 22.6 [95%CI 21.6–23.6] EL.U/mL for HPV-18).[21,24] This and other studies show a similar profile of robust HPV-16/18 immune responses in young women, peaking at 7 mo after initial vaccination with the HPV-16/18 AS04-adjuvanted vaccine and reaching a plateau after approximately 18–24 mo that remained well above natural infection levels.[16,18,19,25,35]

One limitation of this extension study was the open design employed as both participants and investigators were aware of which vaccine had been administered; this is unlikely to have influenced the immunogenicity and efficacy assessments, since laboratory staff was blinded to the treatment allocation, but it may have biased the safety assessment toward increased reporting of AEs in women who received the HPV-16/18 AS04-adjuvanted vaccine. Although this study had a limited sample size, it was sufficient to support consistency with the high efficacy estimates observed in larger studies in different countries. However, inherent to studies of this nature, is the low incidence of the higher grade lesions. Here, this resulted in wide CIs when evaluating more limited cohorts, for instance for data restricted to the extended follow-up period only and for the more stringent histological endpoints. This study was not powered to evaluate VE against CIN3+, which is the intermediate precursor to invasive cervical cancer and provides the most stringent evidence of potential cancer prevention even if CIN2+ is the surrogate endpoint used in licensure trials of HPV vaccines.[36] Similarly, this study was not designed or powered to assess cross-protection of individual non-vaccine HPV types, although we were able to observe efficacy of the vaccine in the prevention of endpoints associated with any high-risk type. Cross-protection of individual HPV types has been shown in the large PATRICIA trial following administration of the HPV-16/18 AS04-adjuvanted vaccine.[23,25] The present study was also limited by the fact that VE was not evaluated by age.

In summary, this study showed high efficacy of the HPV-16/18 AS04-adjuvanted vaccine against cervical lesions and persistent infection associated with HPV-16/18 and other high-risk HPV types in young Japanese women. The overall VE against CIN1+, CIN2+, and CIN3+, irrespective of the HPV type associated with the lesion, was high in all the women who received at least one vaccine dose and in the women who were naïve to HPV infection at baseline. Additionally, the vaccine induced a sustained immune response and was generally well tolerated. These results, which are consistent with those of previous studies, suggest that the implementation of the HPV-16/18 AS04-adjuvanted vaccine could be effective in protecting young Japanese women against cervical cancer.

Materials and Methods

Study design

Between June 2009 and February 2011, women from the initial observer-blind, multicenter, randomized, controlled study (NCT00316693)[27,28] were invited to participate in this open extended follow-up study (NCT00929526), which was conducted in 13 centers in Japan. Eligible women were those who had received at least one dose of either HPV-16/18 AS04-adjuvanted vaccine (HPV vaccine group) or hepatitis A control vaccine (*Aimmugen*™, Kaketsuken; control group) in the initial study, had a normal or low-grade cytology at baseline, and were not pregnant or had terminated pregnancy for more than 3 mo at the enrolment of the extended follow-up study. The

combined initial and extended follow-up study duration was approximately 48 mo.

Ethics committee approval was obtained from independent institutional review boards. Written informed consent was obtained from each woman prior to the performance of any study-specific procedures. This study was conducted in accordance with the guidelines of the International Conference on Harmonization–Good Clinical Practice and the Declaration of Helsinki.

Procedures

Cervical liquid-based cytology samples were collected at the yearly follow-up visits. Cytological examinations were performed using the Bethesda 2001 classification system.[37] A pre-specified clinical management algorithm for abnormal cytology results and colposcopy referral was used, as described previously.[17,27] Histopathological changes on the biopsy and excisional specimens were reviewed by a study panel of 3 pathologists, who were masked to vaccine allocation, using a majority rule, and by a fourth pathologist, who coordinated the review process and ensured that agreement on the location and grade level of the lesion in the tissue was obtained between at least 2 members of the panel. The presence of HPV-DNA in cytology samples and in cervical biopsy or excisional specimens was determined by a broad-spectrum polymerase chain reaction (PCR)-based HPV DNA testing algorithm using the SPF_{10} PCR/DEIA/$LiPA_{25}$ version 1 (Lab Biomedical Products), which was based on amplification of the viral L1 gene using the SPF_{10} primers followed by DNA enzyme immunoassay (DEIA) detection.[38,39] The SPF_{10} PCR/DEIA-positive samples were genotyped for 25 HPV types by the reverse hybridization line probe assay ($LiPA_{25}$), as described previously.[38–40] All HPV positive samples were additionally tested by multiplex type-specific PCR for tissue samples and HPV-16/18 type-specific PCR for cytology samples. Redundant testing using generic SPF_{10} PCR with $LiPA_{25}$, followed by type-specific PCR afforded maximum test sensitivity.[39,41]

A likely causal association between the CIN or cancer lesions and a HPV type was determined using the HPV type assignment algorithm, as described previously.[24] Briefly, if a single type of HPV was found in a lesion by PCR, that HPV type was considered to be associated with the lesion. If more than one type of HPV was detected in a lesion by PCR, the HPV type(s) considered to be associated was based on the HPV type(s) present in at least 1 of the 2 immediately preceding cytology samples. Histopathological endpoints irrespective of the HPV type in the lesion were also evaluated, i.e., including all cases of histopathologically confirmed lesions irrespective of the HPV type detected in the lesion and lesions with no HPV type detected. The association between cytological abnormalities and a HPV type was defined by the detection of that type in the cytology samples. Persistent infection (12-mo definition) was defined as detection of the same HPV type in consecutive samples over a minimum of 10 mo.

Blood samples were taken at yearly visits to evaluate anti-HPV-16 and -18 antibodies by an HPV type-specific ELISA.[20]

SAEs, new-onset chronic diseases (including new-onset autoimmune diseases), medically significant conditions (defined as SAE or adverse events prompting emergency room or physician visits other than those related to common diseases), pregnancy and pregnancy outcomes were assessed throughout the 4-y study period in all women who received at least one dose of vaccine.

Statistical analyses

The TVC included all women who received at least one vaccine dose, regardless of their baseline HPV DNA, cytological status, and serostatus. The TVC-naïve included women from the TVC who did not show signs of current or previous HPV infection at baseline, i.e., women who were DNA negative for 14 high-risk HPV types, seronegative for HPV-16/18 and with a normal cytology at baseline. The ATP-E included women, who received all 3 vaccine doses, complied with protocol procedures, were negative for HPV-DNA of the type analyzed at month 0 and 6, and had a normal or low-grade cytology at baseline.

VE analyses were performed on data from the extended follow-up study (case counting as of the first visit of the extended follow-up period) as well as from the combined initial/extension studies (case counting as of the day after receiving the third dose of vaccine in the initial study for the ATP-E or as of the day after receiving the first dose of vaccine in the initial study for the TVC and the TVC-naïve).

A conditional exact method was used to estimate VE for all clinical endpoints. This method computes an exact CI around the rate ratio (ratio of the event rates in the HPV vaccine vs. control vaccine group) and accounts for a potential imbalance in follow-up time between groups.

The measure of VE (cumulative incidence) was defined as one minus the ratio between the incidence rate in the HPV vaccine group and the incidence rate in the control group, expressed in percentage. The incidence rate was given as the number of cases counted divided by the total follow-up time in years, expressed as per 100 women years.

Immunogenicity analyses were performed on the month 48 ATP-I in the HPV vaccine group, wherein women received all 3 vaccine doses, complied with protocol procedures, and did not acquire HPV-16 or HPV-18 infection during the study. GMTs were calculated with 95% CI. The kinetics of the immune response were evaluated in the ATP-I subjects who were seronegative for the corresponding HPV type at baseline and had data available for each time point (ATP kinetic cohort). Safety and pregnancy outcomes were evaluated in the TVC for the combined initial and follow-up studies period.

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Disclosure of Potential Conflicts of Interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare: R.K. received from the GlaxoSmithKline group of companies support for travel to the investigator meeting for the study; fee for participation at the investigator meeting; financial support

for consultancy as a medical expert. In addition, R.K. received fee from the GlaxoSmithKline group of companies and MSD for expert testimony; payments from the GlaxoSmithKline group of companies, QIAGEN and MSD for lectures including service on speaker bureaus; grants through his institution from the GlaxoSmithKline group of companies, QIAGEN and MSD. H.Y. received from the GlaxoSmithKline group of companies consulting fee as coordinating investigator for the study; support for travel to the investigator meeting for the study. In addition, H.Y. received fees from the GlaxoSmithKline group of companies and MSD for expert testimony as medical advisor; payments from the GlaxoSmithKline group of companies and MSD for lectures including service on speaker bureaus; payments from the GlaxoSmithKline group of companies and MSD for development of educational presentations; travel/accommodations/meeting expenses from the GlaxoSmithKline group of companies and MSD unrelated to activities for this study. M.O., P.S., and F.S. are employed by the GlaxoSmithKline group of companies. M.O. and F.S. have stock options from the GlaxoSmithKline group of companies. F.S. has stock from the GlaxoSmithKline group of companies. W.Q. declared no conflict of interest. L.L. works as clinical consultant from XPE Pharma and Science (Belgium) for GlaxoSmithKline Vaccines (Belgium).

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Supplemental Materials

Supplemental materials may be found here:
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