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Post-hoc analysis of injection-site reactions following vaccination with quadrivalent human papillomavirus vaccine in Japanese female clinical trial participants

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ABSTRACT

Aim: The quadrivalent human papillomavirus (4vHPV) vaccine has demonstrated efficacy and immunogenicity and was generally well tolerated in clinical trials conducted in Japan. We report a detailed safety analysis of injection-site reactions in female Japanese 4vHPV clinical trial participants.

Methods: This post-hoc analysis included data from 2 double-blind, placebo-controlled phase II clinical trials of a 3-dose (Day 1, Month 2, Month 6) regimen of 4vHPV vaccine in Japanese young women aged 18–26 years (N = 1021; NCT00378560) and girls aged 9–17 years (N = 107; NCT00411749). Injection-site and systemic adverse events (AEs) were monitored using vaccination report cards for 15 days after each vaccine dose; serious AEs were reported throughout the trials. Post-hoc analyses of data from these trials were performed to examine details of injection-site AEs, including day of onset, time from onset to resolution, and maximum intensity.

Results: Injection-site AEs were reported by 85.6% of 4vHPV vaccine recipients and 72.4% of placebo recipients, most commonly erythema, pain, pruritus, and swelling (each >5% of 4vHPV vaccine recipients). The majority of injection-site AEs had an onset within 3 days of vaccination and were mild to moderate in intensity; few 4vHPV vaccine recipients reported severe injection-site AEs (2.0% overall). All injection-site AEs resolved, and most (4vHPV: 87.5%; placebo: 92.7%) resolved within 5 days of onset.

Conclusions: Most injection-site reactions are mild or moderate in intensity and of short duration. The 3-dose regimen of 4vHPV vaccine is well tolerated in Japanese female clinical trial participants based on this post-hoc analysis. These results will further support safety communication between healthcare providers and vaccine recipients regarding the HPV vaccine.

Trial registration: Clinicaltrials. gov: NCT00378560 and NCT00411749.

1. Introduction

Human papillomavirus (HPV) is the causal agent for nearly all cervical cancers and a significant portion of vulvar, vaginal, anal, penile, and oropharyngeal cancers, with an estimated 630,000 new cancer cases per year (4.5% of all cancers and 8.6% of cancers in females) attributable to HPV each year globally [1]. Most cases of genital warts are also associated with HPV infection, predominantly caused by HPV types 6 and 11 [2].

HPV-related disease presents a significant public health burden in Japan, with approximately 10,000 women newly diagnosed with cervical cancer and around 2800 deaths reported each year based on national registry data [3]. The incidence and mortality of cervical cancer have been increasing in Japan since the mid-1990s, especially in women of childbearing age (15–39 years) [4].

Bivalent HPV (2vHPV; HPV16/18), quadrivalent HPV (4vHPV; HPV6/11/16/18), and 9-valent (9vHPV; HPV6/11/16/18/31/33/45/52/58) vaccines have been developed to prevent infection and disease related to the most common oncogenic HPV types [5,6] The 2vHPV and 4vHPV vaccines

Abbreviations: 2vHPV, bivalent human papillomavirus; 4vHPV, quadrivalent human papillomavirus; 9vHPV, 9-valent human papillomavirus; AE, adverse event; CI, confidence interval; IQR, interquartile range; SAE, serious adverse event; SD, standard deviation; VLP, virus-like particle; VRC, vaccination report card.

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have potential to prevent approximately 70% of cervical cancers attributable to HPV types 16 and 18, and the 9vHPV vaccine extends protection to 90% of cervical cancers globally, based on epidemiological studies [7]. The 4vHPV and 9vHPV vaccines also protect against genital warts caused by HPV types 6 and 11.

The 2vHPV and 4vHPV vaccines were approved in Japan in 2009 and 2011, respectively. Funding for HPV vaccination in Japan began in 2010 and 2 HPV vaccines were included formally in the National Immunization Program in April 2013. Following the implementation of the National Immunization Program, chronic pain and other symptoms were reported in some vaccine recipients, which were later not confirmed to be related to the vaccinations. Concerns over the safety of the HPV vaccines were rapidly spread via Japanese media and social-media services. Subsequently, the proactive recommendation for the routine use of HPV vaccination was suspended in June 2013. Following suspension, the vaccination rate in Japan dropped from over 70% to less than 1%, and remains low, notwithstanding continued availability for age-eligible girls who elect to receive the vaccine, and in spite of statements from the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) that have affirmed the safety of the HPV vaccine [8–11].

In the United States, despite improvements in the HPV vaccination rate, a lower rate of HPV vaccination coverage is reported compared with other adolescent vaccines [12]. Improving healthcare providers' communication has been identified as a key strategy to increase HPV vaccine uptake. Indeed, prior research suggests that vaccine refusal or delay is common among parents of children and adolescents, frequently due to safety concerns [13,14]. However, relatively little is known about how providers understand or address parental hesitancy specific to HPV vaccine in Japan.

The 4vHPV vaccine clinical program included trials conducted in Japan that confirmed the efficacy and safety profile of 4vHPV vaccine in Japanese participants [15,16]. Efficacy against HPV6/11/16/18-related persistent infection and safety of 4vHPV vaccine in Japanese young women aged 18–26 years (N = 1021) was shown previously to be maintained for approximately 2.5 years following the first vaccination in a phase II, randomized, placebo-controlled study. Moreover, in an open-label study that evaluated the long-term safety and effectiveness (over 48 months) of the 4vHPV vaccine in healthy Japanese women aged 16–26 years (N = 1030), no cases of cervical intraepithelial neoplasia Grade 2 or worse or external genital lesions were reported in the per-protocol population. The vaccine was well tolerated, with no new safety signals throughout the 48-month study period [15,16]. Findings of these studies are consistent with 4vHPV vaccine pivotal trials from other countries [17–20]. In addition, real-world effectiveness and safety data following introduction of HPV vaccines in Japan have been published [21–27]. Safety results were reassuring. Nevertheless, considering the low vaccination rate and safety perceptions surrounding the HPV vaccine, it is expected that healthcare providers' communication must be important in Japan, similar to in the US.

Since the most common vaccine-related adverse events (AEs) are injection-site AEs based on the established safety profile of the 4vHPV vaccine in clinical trials [28], we report a post-hoc analysis of AEs from 2 phase II clinical trials of the 4vHPV vaccine conducted in female participants from Japan. The results will be useful for healthcare professionals to communicate the safety of the HPV vaccines, particularly for discussing local reactions with candidates for vaccination and their parents.

2. Material and methods

2.1. Study design

Safety data from 2 trials conducted in Japan were included in this post-hoc analysis. Study V501-027 (NCT00378560; "Study 027") and Study V501-028 (NCT00411749; "Study 028") were double-blind, placebo-controlled phase II trials of the 4vHPV vaccine in Japanese females aged 18–26 (Study 027; N = 1021) and 9–17 years of age (Study 028; N = 107). Study 027 assessed 4vHPV vaccine efficacy, immunogenicity, and safety in healthy participants who were not pregnant and agreed to use effective contraception during the vaccination stage, had no previous abnormal cervical cytology results, and reported a lifetime history of 4 or fewer male sexual partners. The trial design and primary results have been published [16]. Study 028 was an immunogenicity and safety trial. Participants who were not sexually active, did not plan to become sexually active during the trial, and did not have a temperature ≥37.5 °C at the physical examination prior to the trial were randomized 3:1 to 4vHPV vaccine or placebo at the first trial visit. For both trials, participants with a history of splenectomy or known immune disorder, who were currently receiving immunosuppressives (excluding topical corticosteroid therapy), or who had received periodic treatments with immunosuppressives were excluded. Written informed consent was obtained from each participant or, for minors, their parent or legal representative before trial examination.

In both studies, 4vHPV vaccine (20/40/40/20-μg HPV6/11/16/18 virus-like particles (VLPs) plus aluminum adjuvant 225 μg/0.5 mL) or placebo (aluminum adjuvant 225 μg/0.5 mL) was administered as 0.5-mL intramuscular injections at Day 1, Month 2, and Month 6.

The trials were conducted in accordance with the principles of Good Clinical Practice (GCP), and were approved by the appropriate institutional review/ethics boards and regulatory agencies.

2.2. Safety assessments

Safety and tolerability were assessed in all participants who received at least 1 dose of 4vHPV vaccine or placebo and had available follow-up data. Participants (n = 48) from sites with GCP violations (deficiencies of vaccination records) in Study 027 were excluded from the analysis.

Injection-site AEs, systemic AEs, and vaccine-related AEs were recorded on vaccination report cards (VRCs) on Days 1–15 following each vaccine dose. Vaccine-related serious AEs (SAEs) and any new medical conditions were monitored throughout the trials. AEs were defined as "mild" (awareness of sign or symptom but easily tolerated), "moderate" (discomfort enough to cause interference with usual activity), or "severe" (incapacitating with inability to work or do usual activity) in intensity.

In these post-hoc analyses, the proportions of participants with injection-site AEs were summarized by vaccination group and day of onset relative to vaccination (e.g. day of vaccination = Day 1). Participants who had more than 1 injection-site AE on different days were counted separately for the different days of onset. For a particular day, if 4 or more participants in at least 1 vaccination group had any injection-site AEs, a 95% confidence interval (CI) for the between-group difference in proportion was calculated based on the method of Miettinen and Nurminen [29] Similar analyses were applied for selected specific injection-site AEs (injection-site erythema, pain, pruritus, and swelling).

The time (days) from AE onset to resolution was calculated as: (1) the relative day of resolution minus the relative day of onset for events with duration of ≥24 hours, or (2) duration (hours)/24 for those of <24 hours' duration. The cumulative proportions of participants whose injection-site AEs were resolved were calculated by vaccination group and number of days required for resolution, along with between-group differences in cumulative proportions and associated 95% CIs [29]. Similar analyses were performed by maximum intensity and number of injection-site AEs, and for specific AEs.

For participants in Study 027, subgroup analyses were performed based on age category (18–22 or ≥23 years).

3. Results

3.1. Participants

Of the 1021 participants (4vHPV: 509; placebo: 512) randomized in Study 027, 25 (4vHPV: 8; placebo: 17) did not have available safety data and 48 (4vHPV: 21; placebo: 27) were excluded from this analysis due to

GCP violations [16]. A total of 459 4vHPV vaccine recipients and 453 placebo recipients received all 3 vaccinations, and 432 and 428, respectively, completed the 30-month trial. All participants randomized in Study 028 (N = 107) received the 3-dose vaccination series and completed the trial.

Overall, a total of 562 4vHPV vaccine recipients (Study 027: n = 480; Study 028: n = 82) and 493 placebo recipients (Study 027: n = 468; Study 028: n = 25) were included in this post-hoc analysis.

Participant demographic characteristics were generally well-balanced between the 4vHPV vaccine and placebo groups in both studies and in the pooled population [16] (Table 1).

3.2. Injection-site AEs

The numbers of participants from the pooled population who experienced injection-site AEs between Days 1 and 15 following any vaccination are shown in Table 2. Injection-site pain, erythema, and swelling were the most common (i.e. occurred in >25% of 4vHPV vaccine recipients), and the rates of these AEs were higher in the 4vHPV vaccine group than in the placebo group.

The vast majority of injection-site AEs occurred within the first 3 days following any vaccination, most commonly on the day of vaccination (Day 1) or the following day (Day 2) (Fig. S1). Results were generally consistent when data for Studies 027 and 028 were analyzed separately.

Table 1
Participant characteristics.

	4vHPV vaccine (N = 562)	Placebo (N = 493)
Age, years		
Mean (SD)	21.2 (4.1)	22.4 (3.1)
Median (range)	22.0 (9–26)	23.0 (9–26)
Past medical history, n (%)		
No	285 (50.7)	229 (46.5)
Yes	277 (49.3)	264 (53.5)
Prior medication within 3 days before vaccination (any dose), n (%)		
No	342 (60.9)	276 (56.0)
Yes	220 (39.1)	217 (44.0)

Abbreviations: 4vHPV, quadrivalent human papillomavirus; SD, standard deviation.

Table 2
Summary of injection-site AEs among participants in Studies 027 and 028 (pooled population; Day 1–15 following any vaccination).

	4vHPV vaccine (N = 562)		Placebo (N = 493)	
Vaccination group	n	(%)	n	(%)
Number (%) of participants with 1 or more injection-site AEs	481	(85.6)	357	(72.4)
Pain	466	(82.9)	335	(68.0)
Erythema	182	(32.4)	104	(21.1)
Swelling	162	(28.8)	61	(12.4)
Pruritus	38	(6.8)	12	(2.4)
Hemorrhage	15	(2.7)	2	(0.4)
Discomfort	9	(1.6)	4	(0.8)
Induration	3	(0.5)	1	(0.2)
Warmth	3	(0.5)	3	(0.6)
Anesthesia	2	(0.4)	3	(0.6)
Discoloration	1	(0.2)	0	(0.0)
Hematoma	1	(0.2)	3	(0.6)
Movement impairment	1	(0.2)	0	(0.0)
Paresthesia	0	(0.0)	2	(0.4)
Rash	0	(0.0)	1	(0.2)
Reaction	0	(0.0)	2	(0.4)

n, number of participants in each category; N, number of participants in the safety analysis population.
Safety analysis population: participants who received at least 1 vaccination and have safety data post-vaccination.
Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event.

While the pattern of injection-site AE frequency (67.1%, 65.5%, and 62.5% following vaccine dose 1, 2, and 3, respectively; Table 3) and time of onset (Fig. S2) were generally consistent across the 3 vaccination visits, the rates of injection-site erythema and swelling were higher with increasing 4vHPV vaccine dose number (10.1%, 16.4%, and 20.1% for erythema, and 9.8%, 15.9%, and 18.9% for swelling following vaccine dose 1, 2, and 3, respectively, in the pooled population; Table 3). This trend was not observed in the placebo group.

All injection-site AEs eventually resolved in both studies, and the vast majority resolved within 5 days (4vHPV: 87.5% in the pooled population; Table 4). Injection-site AEs in the 4vHPV vaccine group tended to last slightly longer than in the placebo group, with a median duration of 3.0 (interquartile range [IQR]: 2.0–4.0) days compared with 2.0 (IQR: 1.0–3.0), respectively, in the pooled population. Among 4vHPV vaccine recipients, the median duration was slightly longer in girls 9–17 years of age from Study 028 (3.0 days) compared with young

Table 3
Summary of injection-site AEs by vaccination visit in Studies 027 and 028, following 4vHPV vaccine doses 1, 2, and 3 (pooled population).

	4vHPV vaccine		Placebo	
Vaccination group	n/N	(%)	n/N	(%)
Injection-site AEs				
Dose 1	377/562	67.1	293/493	59.4
Dose 2	363/554	65.5	213/485	43.9
Dose 3	338/541	62.5	209/478	43.7
Injection-site erythema				
Dose 1	57/562	10.1	64/493	13.0
Dose 2	91/554	16.4	46/485	9.5
Dose 3	109/541	20.1	49/478	10.3
Injection-site pain				
Dose 1	357/562	63.5	270/493	54.8
Dose 2	353/554	63.7	201/485	41.4
Dose 3	310/541	57.3	193/478	40.4
Injection-site pruritus				
Dose 1	16/562	2.8	8/493	1.6
Dose 2	15/554	2.7	2/485	0.4
Dose 3	17/541	3.1	3/478	0.6
Injection-site swelling				
Dose 1	55/562	9.8	34/493	6.9
Dose 2	88/554	15.9	23/485	4.7
Dose 3	102/541	18.9	31/478	6.5

n, number of participants with 1 or more AEs; N, number of participants with follow-up for indicated dose.
Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event.

Table 4
Distribution of injection-site AE durations in participants receiving the 4vHPV vaccine from Studies 027 and 028 (pooled population).

	4vHPV vaccine			
			Cumulative[a]	
	n	(%)	n	(%)
Participants in population with follow-up	562			
With 1 or more injection-site AEs	481	(85.6)		
<1 day	28	(5.0)	28	(5.8)
1 day	79	(14.1)	107	(22.2)
2 days	128	(22.8)	235	(48.9)
3 days	106	(18.9)	341	(70.9)
4 days	63	(11.2)	404	(84.0)
5 days	17	(3.0)	421	(87.5)
≥6 days[b]	60	(10.7)	481	(100.0)
Median [IQR] of duration (days)	3.0 [2.0–4.0]			

Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event; IQR, interquartile range.
[a] The denominator of cumulative % is the number of participants with 1 or more injection-site AEs. If a participant had more than 1 injection-site AE, the event with the longest duration was used for the analysis.
[b] Including participants whose injection-site AEs were not resolved or who were lost to follow-up before the resolution of injection-site AEs.

Table 5
Distribution of mild and moderate injection-site AE durations by intensity in participants receiving the 4vHPV vaccine from Studies 027 and 028 (pooled population).

	Mild injection-site AEs		Moderate injection-site AEs	
	n	(%)	n	(%)
Participants with follow-up	562		562	
With 1 or more injection-site AEs	345		125	
<1 day	25	(4.4)	2	(0.4)
1 day	73	(13.0)	5	(0.9)
2 days	95	(16.9)	30	(5.3)
3 days	73	(13.0)	32	(5.7)
4 days	38	(6.8)	24	(4.3)
5 days	9	(1.6)	8	(1.4)
≥6 days[a]	32	(5.7)	24	(4.3)
Median [IQR] of duration (days)	2.0 [1.0–3.0]		3.0 [2.0–5.0]	

The following criteria were used for the severity assessment of injection-site erythema and injection-site swelling: mild, ≤2.5 cm; moderate, >2.5 cm to ≤5.0 cm; severe >5.0 cm.
Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event; IQR, interquartile range.
[a] Including participants whose injection-site AEs were not resolved or who were lost to follow-up before the resolution of injection-site AEs.

women 18–26 years of age from Study 027 (2.0 days); however, a smaller number of participants were analyzed in Study 028 (n = 82) versus Study 027 (n = 480). There was no major difference in the duration of injection-site AEs based on vaccine dose number (Table S1).

Most AEs were mild to moderate in intensity, and the number of 4vHPV vaccine recipients reporting severe injection-site AEs was limited (n = 11 [2.0%] overall; 8 [1.7%] from Study 027 and 3 [3.7%] from Study 028; median duration: 3.0 [IQR: 2.0–7.0]). Mild injection-site AEs tended to be shorter in duration than moderate AEs in 4vHPV vaccine recipients (Table 5; median duration of 2.0 days and 3.0 days, respectively, in the pooled population). Most mild and moderate injection-site AEs had durations of 1–4 days, while 5.7% and 4.3% of 4vHPV vaccine recipients experienced mild and moderate AEs, respectively, that lasted 6 or more days (Table 5). Overall, 90.7% of mild and 80.8% of the moderate AEs among 4vHPV vaccine recipients and 91.9% of moderate and 93.2% of mild AEs among placebo recipients resolved within 5 days (data not shown).

Only 1 injection-site AE had a duration of more than 1 month: a participant who received 4vHPV vaccine in Study 028 experienced a severe AE of injection-site pain after the second vaccination and received diclofenac sodium for 1 day, 60 mg loxoprofen sodium for 1 day, and 120 mg loxoprofen for 5 days. This participant recovered after 52 days and completed the third vaccination.

Subgroup analyses were conducted to evaluate the impact of age on the rates of injection-site AEs (Table 6). In subgroup analyses by participant age in Study 027, there were no major differences in patterns of injection-site AEs among subgroups of participants who were younger (18–22 years of age) versus older (≥23 years of age). In both age groups, most (>79%) AEs were reported within 1 day of vaccination, and most (>83%) lasted 4 days or fewer, with a median duration of 3.0 and 2.0 days in the younger and older subgroup, respectively (Table 6).

There were no major differences in intensity of injection-site AEs between participants with or without medical history (Table S2).

3.3. AE summary

When both injection-site and systemic AEs were considered, 90.6% (n/N = 509/562) of 4vHPV vaccine recipients and 84.2% (n/N = 415/493) of placebo recipients experienced AEs within 15 days of any vaccination in the pooled Study 027 and 028 populations (Table 7). While a greater proportion of 4vHPV vaccine recipients (85.6%; n/N = 481/562) experienced injection-site AEs compared with placebo recipients (72.4%; n/N = 357/493), systemic AEs were reported at similar rates among 4vHPV vaccine (45.4%; n/N = 255/562) and placebo (45.0%; n/N = 222/493) recipients.

There were no deaths or vaccine-related SAEs within 15 days of vaccination. One participant from Study 027 discontinued the trial due to an AE (pyrexia) that was considered by the Investigator to be related to the vaccine. This participant experienced fever of moderate intensity

Table 6
Injection-site AEs by day of onset and AE durations in participants receiving the 4vHPV vaccine from Study 027, in subgroups defined by participant age.

	4vHPV vaccine			
	Participants 18–22 years of age		Participants ≥23 years of age	
	n	(%)	n	(%)
Participants with follow-up	235		245	
With 1 or more injection-site AE	191	(81.3)	218	(89.0)
By day of onset				
Day 1	187	(79.6)	212	(86.5)
Day 2	34	(14.5)	41	(16.7)
Day 3	17	(7.2)	6	(2.4)
Day 4	3	(1.3)	4	(1.6)
Day 5	1	(0.4)	3	(1.2)
Day 6 or later	4	(1.7)	4	(1.6)
By AE duration	Cumulative[a]		Cumulative[a]	
	n	%	n	%
<1 day	17	(8.9)	9	(4.1)
1 day	45	(23.6)	53	(24.3)
2 days	95	(49.7)	119	(54.6)
3 days	138	(72.3)	162	(74.3)
4 days	159	(83.2)	191	(87.6)
5 days	165	(86.4)	201	(92.2)
≥6 days[b]	191	(100.0)	218	(100.0)
Median [IQR] of duration (days)	3.0 [2.0–4.0]		2.0 [2.0–4.0]	

Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event; IQR, interquartile range.
[a] The denominator of cumulative % is the number of participants with 1 or more injection-site AEs. If a participant had more than 1 injection-site AE, the event with the longest duration was used for the analysis.
[b] Including participants whose injection-site AEs were not resolved or who were lost to follow-up before the resolution of injection-site AEs.

Table 7
Summary of AEs among participants in Studies 027 and 028 (pooled population; Days 1–15 following any vaccination).

	4vHPV vaccine (N = 562)		Placebo (N = 493)	
	N	(%)	n	(%)
With no AEs	53	(9.4)	78	(15.8)
With 1 or more AEs	509	(90.6)	415	(84.2)
Injection-site AEs	481	(85.6)	357	(72.4)
Systemic AEs	255	(45.4)	222	(45.0)
With vaccine-related[a] AEs	491	(87.4)	366	(74.2)
Injection-site AEs	480	(85.4)	357	(72.4)
Systemic AEs	75	(13.3)	53	(10.8)
With SAEs	3	(0.5)	1	(0.2)
With vaccine-related[a] SAEs	0	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)
Discontinued due to AE	1	(0.2)	0	(0.0)
Discontinued due to vaccine-related[a] AE	1	(0.2)	0	(0.0)
Discontinued due to SAE	0	(0.0)	0	(0.0)
Discontinued due to vaccine-related[a] SAE	0	(0.0)	0	(0.0)

n, number of participants in each category; N, number of participants in the safety analysis population.
Safety analysis population: participants who received at least 1 vaccination and have safety data post-vaccination.
Abbreviations: 4vHPV, quadrivalent human papillomavirus; AE, adverse event; SAE, serious adverse event.
[a] Vaccine-related AEs are AEs determined by the investigator to be possibly, probably, or definitely vaccine-related.

on the day after the first 4vHPV vaccination (Day 1) and recovered 7 days after vaccination.

Vaccine-related systemic AEs were reported by 75 (13.3%) and 53 (10.8%) 4vHPV vaccine and placebo recipients, respectively. The most common vaccine-related systemic AEs (rate of ≥1%) among 4vHPV vaccine recipients were headache (3.7%, n/N = 21/562), fever (5.7%, n/N = 32/562), and fatigue (1.2%, n/N = 7/562); these AEs were reported by 2.4% (n/N = 12/493), 3.7% (n/N = 18/493), and 2.0% (n/N = 10/493), respectively, of placebo recipients.

4. Discussion

This post-hoc analysis suggests that the 4vHPV vaccine is generally well tolerated in female Japanese clinical trial participants. Most injection-site AEs were mild or moderate in intensity, and most occurred within 2 days of a vaccination (i.e. by Day 3). The vast majority of injection-site AEs resolved within 5 days of 4vHPV vaccine administration (median: 3.0 days). Only 1 AE of injection-site pain persisted for more than 1 month and resolved after 52 days.

Injection-site AEs represent general reactions to vaccination, which may be mediated by hypersensitivity reactions. These local inflammatory responses are thought to follow the formation of immune complexes between the circulating antibody and the injected antigen. The longer duration of injection-site AEs and higher intensity of AEs in the younger population included in Study 028 (girls 9–17 years of age) could reflect the higher immunogenicity in this age group compared with the older population in Study 027 (young women 18–26 years of age). In previous 4vHPV vaccine clinical trials, rates of injection-site AEs were 64% and 60% in Japanese boys and men, respectively, while geometric mean titer ratios (boys versus men) for anti-HPV6/11/16/18 antibodies were 1.25–3.05 [30,31]. Similar results were observed in studies of the 9vHPV vaccine in Japanese girls and women [32,33]. Most injection-site AEs were mild and moderate in both girls and young women in Study 027 and 028, and participants recovered within 5 days; these results were also consistent with the severity and duration of reactions observed in Japanese boys and men receiving the 4vHPV vaccine, as well as Japanese girls and women given the 9vHPV vaccine [30–33]. An early onset of injection-site AEs was also observed in the placebo group, with most AEs occurring on the day of vaccination. As most AEs occurred on the same day they may have been reactions to the free form of adjuvant, as in a global clinical trial, lower rates of injection-site AEs were observed with a saline placebo [34]. In addition, higher rates of injection-site AEs were reported with the 9vHPV vaccine compared with the 4vHPV vaccine in a global pivotal efficacy trial, as might be expected given that the 9vHPV vaccine contains higher amounts of HPV VLP antigens and amorphous aluminum hydroxyphosphate sulfate adjuvant [35].

Based on systematic monitoring of HPV vaccine safety, the WHO GACVS considers HPV vaccines extremely safe and, to date, has not identified any safety issues that would alter its recommendations for the use of HPV vaccines [9–11]. However, in Japan, the proactive recommendation for routine use of HPV vaccination in the national immunization program was suspended in 2013 following the occurrence of chronic pain and other symptoms in some vaccine recipients which were not confirmed to be related to the vaccine [8,10]. The active recommendation for HPV vaccine remains suspended in Japan as of November 2019, and the vaccination rate is extremely low (0.1–4.1% for girls born in 2000–2003 in Sakai City, Osaka, Japan, based on a 2017 report) [8]. Based on a survey of 29,846 women in Nagoya City, Japan, which was conducted to examine the relationship between HPV vaccination and suspected AEs, no causal relationship between HPV vaccine and the development of 24 suspected AEs has been found [25]. A survey by Yagi et al. [36] showed that only 4.1% of Japanese mothers would likely encourage HPV vaccination of their daughters, without any other preconditions, if the governmental recommendation of HPV vaccination was reinstated. The current analysis of two clinical trials in Japan has found no evidence for severe or prolonged injection-site reactions following HPV vaccine and provides robust evidence for providers to enable young women and their carers to be reassured.

This analysis of AEs was post-hoc in nature and, therefore, encompasses the inherit limitations of this type of analysis. The studies were not powered to evaluate rare AEs. However, VRC-aided reporting was used in both Studies 027 and 028, and injection-site AEs were reported more frequently than in a separate clinical trial in Japanese young women that did not utilize VRCs [15]. Rates of injection-site reactions were generally similar to those observed in studies outside Japan that used VRC-aided reporting [20]. In addition, these trials enrolled healthy participants without a history of immune disorder, and immunosuppresives and simultaneous vaccination with other vaccines were prohibited. Therefore, this post-hoc analysis does not take these factors into account.

The results of this post-hoc analysis of 2 clinical trials further support that the 3-dose regimen of 4vHPV vaccine is well tolerated in Japanese girls and young women. Most injection-site reactions after vaccination are mild or moderate in intensity and of short duration.

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CRediT authorship contribution statement

Shinya Murata: Conceptualization, Methodology, Formal analysis, Writing - review & editing. **Masayoshi Shirakawa:** Data curation, Formal analysis, Writing - review & editing. **Yoshie Sugawara:** Conceptualization, Methodology, Writing - review & editing. **Michiko Shuto:** Formal analysis, Writing - review & editing. **Miyuki Sawata:** Formal analysis, Writing - review & editing. **Yoshiyuki Tanaka:** Conceptualization, Methodology, Investigation, Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors are employees of MSD K·K., Tokyo, Japan and may own stock or stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

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Appendix A. Supplementary data

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