J Infect Chemother 25 (2019) 520–525

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Effectiveness on high-grade cervical abnormalities and long-term safety of the quadrivalent human papillomavirus vaccine in Japanese women☆

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ARTICLE INFO

Article history:
Received 10 September 2018
Received in revised form
17 January 2019
Accepted 20 February 2019
Available online 15 March 2019

Keywords:
Human papillomavirus
Quadrivalent vaccine
Effectiveness
Safety
Japan

ABSTRACT

This study for the first time assessed quadrivalent human papillomavirus (qHPV) vaccine effectiveness against HPV6/11/16/18-related high-grade cervical disease in Japanese women (16–26 years old), as previously demonstrated in overseas trials, and vaccine safety in a longer term (48-month) open-label study (NCT01544478). Participants received three doses of qHPV vaccine (Day 1, Month 2, Month 6). Effectiveness endpoints, assessed in the per-protocol population, included incidence of HPV6/11/16/18-related cervical intraepithelial neoplasia (CIN) Grade 2 or worse (CIN Grade 2 and 3, adenocarcinoma in situ, and/or cervical cancer) as primary endpoint and incidence of external genital lesions (EGLs). Disease related to other high-risk HPV types was also assessed. Adverse events (AEs) and serious AEs (SAEs) were collected from Days 1–15 after any vaccination; vaccine-related SAEs, deaths, and new medical conditions were collected throughout the study. A total of 1030 women received at least one vaccination. No cases of CIN2 or worse or EGLs were reported in the per-protocol population. Injection site-related AEs were reported in 14.5% of participants; most were mild and resolved within 15 days. Vaccine-related systemic AEs occurred in 8.6% of participants, most commonly headache (2.3%), malaise (1.7%), and pyrexia (1.3%). There were no vaccine-related SAEs; one participant discontinued due to a vaccine-related AE of mild uticaria. Overall, qHPV vaccine effectiveness against HPV6/11/16/18-related high-grade cervical disease and EGLs was indicated in Japanese women. The vaccine was well-tolerated, without new safety signals throughout the 48-month study period. Findings are consistent with overseas qHPV vaccine pivotal trials.

Clinical trial registry: clinicaltrials.gov; NCT01544478.

1. Introduction

Human papillomavirus (HPV) infection causes benign, pre-cancerous, and malignant disease, including cancers and pre-cancers of the cervix, vulva, vagina, anus, penis, tonsil, and base of the tongue, as well as anogenital warts and recurrent respiratory papillomatosis [1]. HPV is the cause of nearly all cervical cancers,

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https://doi.org/10.1016/j.jiac.2019.02.012

which represent the fourth most common cancer among women and the fourth most common cause of female cancer-related mortality worldwide [2].

In Japan, cervical cancer is the tenth most common female cancer and cause of female cancer-related mortality, while among women aged 15–44 years, it is the second leading cancer in terms of both incidence and mortality [3]. An estimated that 9390 cervical cancer cases, and more than 3600 cervical cancer-related deaths occur annually in Japan, based on 2012 data [3]. In a recent study, HPV types 16 and 18 account for the majority (65.4% single-type infections) of invasive cervical cancers in Japan [4].

Prophylactic HPV vaccination represents a unique opportunity to reduce the burden of HPV-associated disease, and at least 80 countries have implemented national HPV immunization programs [5]. The quadrivalent HPV (qHPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine (Gardasil™, MSD) is approved in more than 130 countries, including Japan, where it was approved in July 2011. Based on global epidemiology data, the qHPV vaccine has potential to prevent the approximately 70% of cervical cancers attributable to HPV 16/18, and more than 90% of cases of genital warts, which are predominately attributable to HPV types 6 and 11 [6,7]. The qHPV vaccine demonstrated efficacy and safety in multiple randomized, placebo-controlled clinical trials and in real-world studies [8–10]. In the pivotal Phase 3 trials, the qHPV vaccine demonstrated 98%–100% efficacy in reducing the incidence of HPV 6/11/16/18-related anogenital disease [11] and HPV 16/18-related high-grade cervical disease [12] among susceptible young women. In the 10 years following introduction of the HPV vaccination, real-world evidence demonstrated significant reductions (up to 90%) in the prevalence of HPV 6/11/16/18-related infections among young women falling into age groups targeted by national vaccination programs, particularly in countries with high vaccine uptake [9]. Clinical trial data, including those from long-term follow up studies, and post-licensure safety data collected through active and passive safety surveillance programs support the favorable safety profile of the qHPV vaccine [10,13].

Efficacy against HPV 6/11/16/18-related persistent infection and safety of qHPV 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 2, randomized, placebo-controlled study [14]. Moreover, a recently published observational study of cervical cytology results from 2425 young Japanese women with or without HPV vaccination showed that the rate of atypical squamous cells of undetermined significance (ASC-US) or worse was 0.242% (1/413) with HPV vaccination and 2.04% (41/2012) without HPV vaccination [15].

This article reports the outcomes of an open-label study (NCT01544478) that evaluated the long-term safety and effectiveness (over 48 months) of the qHPV vaccine on the incidence of HPV 6/11/16/18-related cervical intraepithelial neoplasia (CIN) Grade 2 or worse in healthy Japanese women aged 16–26 years old. This study was conducted as part of the pharmacovigilance plan for the qHPV vaccine and regulatory commitment following its launch in Japan.

2. Materials and methods

2.1. Study design and population

Study V501-110 (NCT01544478) was a 48-month, open-label, single-arm descriptive trial of a three-dose qHPV vaccine regimen conducted at 21 centers in Japan between November 25, 2011 (first participant visit) and December 14, 2016 (database lock) (Fig. 1). Participants were healthy Japanese women aged 16–26 years, who were not pregnant and agreed to use effective contraception through Month 7 of the study. Participants were required to refrain from sexual intercourse for 2 days prior to any scheduled visit that included a pelvic exam; those who had sexual intercourse in the 2 weeks prior to enrollment must have been using effective contraception. Women with five or more lifetime sexual partners and those with a history of external genital warts, vaginal warts, positive HPV test, abnormal Papanicolaou (Pap) test, or abnormal cervical biopsy were excluded. Women with no sexual lifetime sexual partners were required to be at least 18 years of age and have plans to become sexually active within the first 3 months of the study to be eligible to participate. Women who had received any HPV vaccine previously were excluded.

The primary endpoint was incidence of CIN 2/3, adenocarcinoma in situ (AIS), and/or cervical cancer related to HPV 6, 11, 16, or 18. The incidence of external genital lesions (EGLs; condyloma acuminata, vulvar intraepithelial neoplasia [VIN] 1/2/3, vaginal intraepithelial neoplasia [VaIN] 1/2/3, vulvar cancer and/or vaginal cancer) related to HPV 6, 11, 16, or 18 was a pre-specified exploratory endpoint. The incidence of CIN 1/2/3, AIS, and/or cervical cancer relative to 10 additional high-risk HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and the incidence of EGLs related to the other 10 high-risk HPV types were also assessed. Safety endpoints were adverse events (AEs) and serious AEs (SAEs) occurring between Days 1 and 15 following each study vaccination and vaccine-related SAEs, deaths, and new medical conditions that occurred during the entire study period. Vaccination report cards were not used in this study.

The study was conducted in accordance with principles of Good Clinical Practice and the Declaration of Helsinki. It was also approved by the appropriate institutional review boards and regulatory agencies; all participants provided written informed consent.

2.2. Vaccination and follow-up

The qHPV vaccine was administered as a series of three, 0.5-mL intramuscular injections at Day 1, Month 2, and Month 6. Participants were observed for at least 30 min after each vaccination for any immediate reaction, particularly evidence of allergic phenomena. Pregnancy testing was conducted prior to each vaccine dose (urine test sensitive to 25 mIU/mL human chorionic gonadotropin). Any women found to be pregnant at the Day 1 visit could not participate in the study. For those women who became pregnant after receiving one or two vaccinations, study visits and vaccinations were delayed until after resolution of the pregnancy.

Gynecological examinations were performed, and ThinPrep™ Pap tests for liquid-based cytology Pap testing were collected at Day 1 and Months 7, 12, 24, 36, and 48. Labial/vulvar/perineal and perianal (LVPP) and endo-/ectocervical (EEC) specimens were collected for HPV PCR assays at Day 1 and Month 7. Cytology specimens were evaluated at a central laboratory using The Bethesda System-2001. For diagnoses of ASC-US, reflex testing for high-/low-risk HPV probes (Digene Hybrid Capture II™ Assay) was performed on residual ThinPrep material at the Central Laboratory. Participants were referred for biopsy and definitive therapy based on the protocol triage algorithm. EGLs and vaginal lesions suspected to be possibly, probably, or definitely HPV-related were biopsied, and samples were analyzed at the Central Laboratory. Tissue obtained via biopsy or definitive therapy was tested for HPV types and adjudicated by a pathology panel to provide a pathology diagnosis for study purposes. Colposcopic standardization training was conducted in order to standardize colposcopy and biopsy practices, and provide a guide for all aspects of the protocol-related colposcopy and histological sampling.

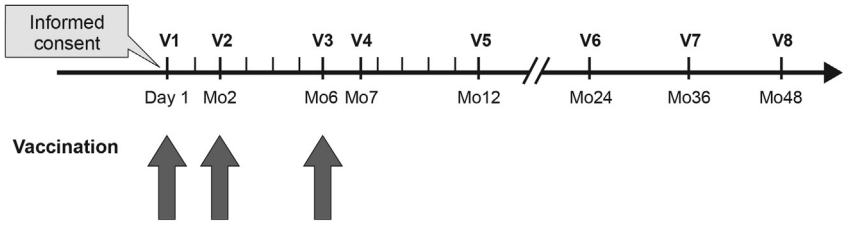

Fig. 1. Study design.

Safety (reported AEs) was reviewed and medical history updated at follow-up visits at Months 2, 6, 7, 12, 24, 36, and 48. All pregnancies in which conception was estimated to occur between Day 1 and Month 48 of the study were recorded and followed for outcomes.

2.3. Statistical analyses

The primary effectiveness analysis was conducted in the per-protocol efficacy (PPE) population who: (1) were seronegative on Day 1 and PCR-negative from Day 1 through Month 7 for the HPV type being analyzed; (2) received all three doses of the correct clinical material within 1 year; (3) had at least one follow-up visit after Month 7; and (4) had no protocol violations that could interfere with the evaluation of effectiveness.

Supportive effectiveness analyses were conducted in the following additional modified intention-to-treat populations, with cases counted starting at Day 1. The HPV-naïve to the relevant type (HNRT) population included participants who were seronegative and PCR-negative to the relevant vaccine HPV type(s) at baseline, received at least one vaccination, and who had any follow-up visit after Day 1. The full analysis set (FAS) included all participants who received at least one vaccination and had any follow-up visit, regardless of initial HPV serology and PCR status. Endpoints due to any HPV type were assessed in the generally HPV-naïve (GHN) population who: (1) were sero- and PCR-negative to all vaccine HPV types (6, 11, 16, and 18) and PCR-negative to all non-vaccine HPV types (based on available PCR assays) at baseline; (2) had a negative baseline Pap test result; (3) received at least one vaccination and (4); and had at least one follow-up visit after Day 1. For the effectiveness analyses endpoints, point estimates, and exact 95% confidence intervals (CI) for incidence rates were computed based on Poisson distributions.

Safety was assessed in all participants who received at least one vaccination and had available safety data. The primary outcome of interest was the incidence of vaccine-related SAEs occurring any time during the study.

3. Results

3.1. Participants

Participant disposition is presented in Table 1. A total of 1030 participants 17–26 years of age (mean 22.9 years) received at least one vaccination, 1019 (98.9%) completed the three-dose vaccination series, and 912 (88.5%) completed the study (Month 48). Most discontinuations were related to participants who were lost to follow-up or withdrew consent; one participant discontinued due to mild urticaria.

Baseline demographic characteristics and HPV status are presented in Table 2. A total of 9.8% of participants were seropositive to HPV 6, 11, 16, or 18, and 5.5% were PCR-positive to HPV 6, 11, 16, or 18 at baseline.

3.2. Effectiveness

In the PPE population, there were no cases of HPV 6/11/16/18-related cervical disease, including low-grade (CIN 1) and high-grade (CIN 2, 3, or worse) cervical disease (incidence: 0.0/100 person-years [95% CI: 0.0, 0.1]) (Table 3). In addition, no cases of

Table 1
Disposition of participants.

	N (%)
Participants	1030 (100.0)
Vaccinated at	
Vaccination 1	1030 (100.0)
Vaccination 2	1026 (99.6)
Vaccination 3	1019 (98.9)
Study disposition	
Completed	912 (88.5)
Discontinued	118 (11.5)
AE	1 (0.1)
Death	1 (0.1)
Lost to follow-up	48 (4.7)
Physician decision	15 (1.5)
Pregnancy	1 (0.1)
Withdrawal by participant	52 (5.0)

Abbreviations; AE: adverse event.

Table 2
Baseline demographic characteristics and HPV status.

Characteristic at Day 1 (qHPV)	Vaccination group (N = 1030)
Gender, % (m)	
Female	100% (1030)
Age (years)	
Mean	22.9
SD	2.2
Median	23
Range	17–26
Race, % (m)	
Asian	100% (1030)
Serostatus, % (m/n)	
Positive to HPV 6/11/16/18	9.8% (101/1030)
Positive to HPV 6	4.3% (44/1030)
Positive to HPV 11	0.7% (7/1030)
Positive to HPV 16	4.7% (48/1030)
Positive to HPV 18	2.1% (22/1030)
PCR status, % (m/n)	
Positive to HPV 6/11/16/18	5.5% (56/1023)
Positive to HPV 6	1.3% (13/1023)
Positive to HPV 11	0.2% (2/1023)
Positive to HPV 16	3.4% (35/1022)
Positive to HPV 18	1.2% (12/1023)

Abbreviations; HPV: human papillomavirus, m: number of subjects belonging to the indicated category, n: number of subjects with non-missing Day 1 (qHPV) status corresponding to the indicated HPV type, N: number of subjects in the indicated vaccination group who received at least one dose of the qHPV vaccine, PCR: polymerase chain reaction, qHPV: quadrivalent human papillomavirus [Types 6, 11, 16, 18] recombinant vaccine, SD: standard deviation.
Day 1 (qHPV) is the day of injection of Dose 1 of the qHPV vaccine.
Unless otherwise indicated, the percentages shown were calculated as 100*(m/N).

Table 3
Effectiveness of qHPV vaccine against HPV 6/11/16/18-related cervical lesions and EGLs, cumulative incidence (PPE population).

	n	Number of cases	Person-years at risk	Incidence per 100 personyears at risk	95% CI
HPV 6/11/16/18-related CIN	967	0	3034.6	0.0	(0.0, 0.1)
CIN 2/3 or worse	967	0	3034.6	0.0	(0.0, 0.1)
CIN 1	967	0	3034.6	0.0	(0.0, 0.1)
HPV 6/11/16/18-related EGLs	970	0	3037.4	0.0	(0.0, 0.1)
Condyloma acuminate	970	0	3037.4	0.0	(0.0, 0.1)
VIN 1 or worse	970	0	3037.4	0.0	(0.0, 0.1)
VaIN 1 or worse	970	0	3037.4	0.0	(0.0, 0.1)

Abbreviations; CI: confidence interval, CIN: cervical intraepithelial neoplasia, EGL: external genital lesion, HPV: human papillomavirus, PPE: per-protocol efficacy, VaIN: vaginal intraepithelial neoplasia, VIN: vulvar intraepithelial neoplasia.

EGL, including condyloma acuminate, VIN1 or worse, VaIN 1 or worse (incidence: 0.0/100 person-years [95% CI: 0.0, 0.1]), were recorded in the PPE population (Table 3).

The incidence of HPV 6/11/16/18-related high-grade cervical diseases (CIN 2 or worse) in the FAS population was 0.4/100 person-years (95% CI: 0.2, 0.6; 14 events) (Table 4); no events were reported in the HNRT or GHN populations (incidence: 0.0/100 person-years [95% CI: 0.0, 0.1] for each; Supplementary Table 1). All cases of CIN 2 or worse that occurred in the FAS were among participants who were PCR-positive to relevant HPV types at baseline.

A total of 73 cases of CIN 1/2/3, AIS, and/or cervical cancer related to any of the examined high-risk HPV types were reported in the FAS population (incidence: 2.0/100 person-years [95% CI: 1.6, 2.5]) (Table 5). No cases were reported in the PPE, HNRT, or GHN populations (incidence: 0.0/100 person-years [95% CI: 0.0, 0.1] for each). Of the 73 events in the FAS, 27 were graded severe (CIN 2 or worse; incidence: 0.7/100 person-years [95% CI: 0.5, 1.1]). There were no cases of AIS or cervical cancer. Cases of CIN 1 or worse in the FAS population were most frequently related to HPV 56 (incidence: 0.5/100 person-years [95% CI: 0.3, 0.7]; 17 cases), HPV 52 (incidence 0.4/100 person-years [95% CI: 0.2, 0.7]; 16 cases), and HPV 16 (incidence 0.4/100 person-years [95% CI: 0.2, 0.6); 14 cases).

3.3. Safety

A summary of AEs experienced by participants throughout the study is presented in Table 6. Vaccine-related AEs with an incidence of 1% or greater included injection-site pain, swelling, itching, and erythema; headache; malaise; and pyrexia (Table 7). The incidence of injection-site–related AEs reported from Day 1 to Day15 was 14.5% (149/1029 participants). All of these AEs were mild, with the exception of one moderate AE of injection-site pain, and most resolved within 15 days of occurrence.

Vaccine-related systemic AEs occurred in 8.6% of participants within 15 days of vaccination and most commonly included headache (2.3%), malaise (1.7%), and pyrexia (1.3%).

A total of eight SAEs were reported throughout the study, which included: induced abortion in four participants; and spontaneous abortion, peritonsillitis, subarachnoid hemorrhage, and fetal malpresentation in one participant each. These events were considered not related to the vaccine by investigators. The SAE of subarachnoid hemorrhage, which occurred 128 days after the third qHPV vaccine dose, resulted in death (death occurred 140 days after the third vaccination). The participant who died was a 19-year-old Japanese female with asthma. She did not have any other AEs except for subarachnoid hemorrhage during the study.

4. Discussion

No cases of CIN 2/3, AIS, and/or cervical cancer related to HPV 6, 11, 16, or 18 were reported through 3.5 years of follow-up in healthy Japanese women aged 16–26 years old who received a three-dose regimen of qHPV vaccine and were naïve to these HPV types during immunization (incidence: 0.0/100 person-years [95% CI: 0.0, 0.1]). These findings are generally consistent with observations in other qHPV vaccine clinical studies that were conducted outside Japan [12,16] and in Japan [14]. The vaccine was generally safe and well tolerated in this population. No vaccine-related SAEs or serious injection-site AEs were reported. The majority of injection-site AEs were mild in intensity. Overall, the qHPV vaccine appeared

Table 4
Effectiveness of qHPV vaccine against HPV 6/11/16/18-related cervical lesions, cumulative incidence (FAS).

Endpoint	Vaccination group (N = 1030)				
	n	Number of cases	Person- years at risk	Incidence per 100 person-years at risk	95% CI
HPV 6/11/16/18-related CIN 2/3 or worse	1015	14	3747.6	0.4	(0.2, 0.6)
By HPV type					
HPV 6-related CIN 2/3 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
HPV 11-related CIN 2/3 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
HPV 16-related CIN 2/3 or worse	1015	14	3747.6	0.4	(0.2, 0.6)
HPV 18-related CIN 2/3 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
By endpoint type (HPV 6/11/16/18-related)					
CIN (any grade)	1015	15	3742.6	0.4	(0.2, 0.7)
CIN 1	1015	5	3747.8	0.1	(0.0, 0.3)
CIN 2 or worse	1015	14	3747.6	0.4	(0.2, 0.6)
CIN 2	1015	9	3749.3	0.2	(0.1, 0.5)
CIN 3	1015	10	3751.8	0.3	(0.1, 0.5)
AIS	1015	0	3753.9	0.0	(0.0, 0.1)
Cervical cancer	1015	0	3753.9	0.0	(0.0, 0.1)

Abbreviations; AIS: adenocarcinoma in situ, CI: confidence interval, CIN: cervical intraepithelial neoplasia, FAS: full analysis set, HPV: human papillomavirus, n: number of subjects in the indicated analysis population, N: number of subjects in the indicated group who received at least one dose of the qHPV vaccine, qHPV: quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine.

Table 5
Effectiveness of qHPV vaccine against high-risk HPV type-related CIN 1 or worse cumulative incidence (FAS).

Endpoint	Vaccination group (N = 1030)				
	n	Number of cases	Person- years at risk	Incidence per 100 person-years at risk	95% CI
Any HPV type-related CIN 1 or worse	1015	73	3641.6	2.0	(1.6, 2.5)
By HPV Type					
HPV 6-related CIN 1 or worse	1015	2	3748.9	0.1	(0.0, 0.2)
HPV 11-related CIN 1 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
HPV 16-related CIN 1 or worse	1015	14	3746.3	0.4	(0.2, 0.6)
HPV 18-related CIN 1 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
HPV 31-related CIN 1 or worse	1015	3	3748.2	0.1	(0.0, 0.2)
HPV 33-related CIN 1 or worse	1015	2	3752.1	0.1	(0.0, 0.2)
HPV 35-related CIN 1 or worse	1015	0	3753.9	0.0	(0.0, 0.1)
HPV 39-related CIN 1 or worse	1015	2	3748.3	0.1	(0.0, 0.2)
HPV 45-related CIN 1 or worse	1015	1	3750.1	0.0	(0.0, 0.1)
HPV 51-related CIN 1 or worse	1015	7	3742.4	0.2	(0.1, 0.4)
HPV 52-related CIN 1 or worse	1015	16	3740.2	0.4	(0.2, 0.7)
HPV 56-related CIN 1 or worse	1015	17	3713.5	0.5	(0.3, 0.7)
HPV 58-related CIN 1 or worse	1015	11	3740.7	0.3	(0.1, 0.5)
HPV 59-related CIN 1 or worse	1015	2	3750.4	0.1	(0.0, 0.2)
By endpoint type (any HPV type-related)					
CIN (any grade)	1015	73	3641.6	2.0	(1.6, 2.5)
CIN 1	1015	55	3656.3	1.5	(1.1, 2.0)
CIN 2 or worse	1015	27	3732.0	0.7	(0.5, 1.1)
CIN 2	1015	20	3737.2	0.5	(0.3, 0.8)
CIN 3	1015	13	3746.2	0.3	(0.2, 0.6)
AIS	1015	0	3753.9	0.0	(0.0, 0.1)
Cervical cancer	1015	0	3753.9	0.0	(0.0, 0.1)

Abbreviations; AIS: adenocarcinoma in situ, CI: confidence interval, CIN: cervical intraepithelial neoplasia, FAS: full analysis set, HPV: human papillomavirus, n: number of subjects in the indicated analysis population, N: number of subjects in the indicated group who received at least one dose of the qHPV vaccine, qHPV: quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine.

efficacious and generally well tolerated among Japanese women 16–26 years of age through 3.5 years of follow-up, consistent with findings from the global clinical trial program.

This was an open-label study; however, it is unlikely for this to have influenced the effectiveness assessment, as all diagnoses were made by the HPV vaccine pathology panel, who prepared their report without knowledge of the participant demographic information, including whether a subject was vaccinated or not. The laboratory staff who performed the PCR testing were also not aware of the participant demographic information. The open-label design had potential to bias the safety findings; because all subjects received qHPV vaccine, there is a possibility that AEs were over-reported. As a post-marketing study, use of placebo was not feasible and this study lacked a control group. Therefore, no direct comparisons were conducted within this study. However, the observed placebo incidence rate for HPV 6/11/16/18-related CIN 2/3 or AIS were 0.44 per 100 person-years, with vaccine efficacy of 97.2% in the global FUTURE II clinical study (unpublished data), where the composite endpoint of HPV 16/18-related CIN 2 or worse was a primary endpoint [12]. Similarly, in a pooled analysis of three global randomized clinical trials, the incidence of CIN 2 or worse was 0.5/100 person-years in the placebo group compared with 0.0 in the qHPV vaccine group (98.2% efficacy) [16]. The incidence rate in this study was 0.0/100 person-years [95% CI: 0.0, 0.1]. The protection afforded by the qHPV vaccine appears to be durable for at least 10 years; in a 12-year follow-up of participants from the FUTURE II study, there were no breakthrough cases of HPV 16/18-related CIN 2 or worse, with effectiveness >90% maintained for at least 10 years [17].

In a recent epidemiological study, the most common HPV types associated with cervical cancer in Japan were HPV 16, 18, 31, 52, and 58; single-type infections with these types were detected in 48.7%, 16.7%, 4.9%, 11.8%, and 3.9% of invasive cervical cancers, respectively [4]. Among the 14 high-risk HPV types assessed in this study, most cases of CIN 1 or worse that occurred in the FAS were related to HPV 16, 52, 56, and 58, consistent with the high relative prevalence of HPV 16, 52 and 58 in Japan [4]. HPV vaccines have been discussed to afford some cross-protection against a few non-vaccine types. However, cross-protection against disease related to non-vaccine HPV types appears to be of limited and uncertain clinical

Table 6
Summary of AEs during the entire study period.

	N	%
Participants in population	1029	100
Participants with ≥1 AEs	344	33.4
Injection site	149	14.5
Non-injection site	249	24.2
Participants with no AEs	685	66.6
Participants with vaccine-related AEs	213	20.7
Injection site	149	14.5
Non-injection site	89	8.6
Participants with SAEs	8	0.8
Participants with vaccine-related SAEs	0	0.0
Participants who died	1	0.1
Participants who discontinued due to AEs	1	0.1
Participants who discontinued due to vaccine-related AEs	1	0.1
Participants who discontinued due to vaccine-related SAEs	0	0.0

Abbreviations; AE: adverse event, SAE: serious adverse event.

Table 7
qHPV vaccine-related AEs occurring in ≥1% of participants (Days 1–15 following vaccination).

	N	%
Participants in population	1029	100
Participants with injection-site vaccine-related AEs		
Injection-site pain	118	11.5
Injection-site swelling	40	3.9
Injection-site itching	24	2.3
Injection-site erythema	12	1.2
Participants with non-injection-site vaccine-related AEs		
Headache	24	2.3
Malaise	18	1.7
Pyrexia	13	1.3

Abbreviations; AE: adverse event.

significance, and may have limited duration of protection [18]. While the qHPV vaccine does not confer protection against HPV 52, 56, or 58, a nine-valent vaccine has been developed that covers HPV 31/33/45/52/58 in addition to the four types covered by the qHPV vaccine and may be particularly useful in regions with high prevalence of the additional oncongenic types [19].

The risk of the HPV infection and cervical cancer continues to increase in Japan for sexually active young females who refrain from vaccination [20]. The World Health Organization Global Advisory Committee on Vaccine Safety monitors vaccine safety based on post-licensure surveillance data and has concluded that evidence available (as of May 2017) does not point to any safety concerns with the use of HPV vaccine [21]. In conclusion, the data reported herein further support implementation of widespread vaccination for HPV-related disease prevention, including Japan.

Funding

This work was supported by Merck & Co., Inc., Kenilworth, NJ, USA.

Medical writing assistance was provided by Erin Bekes, PhD, of Complete Medical Communications, Hackensack, NJ. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA. The authors would like to thank the other investigators in this study.

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Conflicts of interest

MS received research funding from the study sponsor, MSD K.K., to conduct this research.

EM received grants and lecture fees from the study sponsor, MSD K.K.

YS received research funding from the study sponsor, MSD K.K., to conduct this research.

KA, NK, HN, and SA have nothing to disclose.

S-RH, AW, SM, MS and YT are current or former employees of MSD K.K., a group of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA, and may own stock and/or stock options.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2019.02.012.

References

[1] Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;30(Suppl 5):F12–23.

[2] Bruni L, Barrinuevo-Rosas L, Albero G, Serrano B, Mena M, Gomez D, et al. Human papillomavirus and related diseases report: world summary report. ICO Information Centre on HPV and Cancer (HPV Information Centre); 2017.

[3] Bruni L, Barrinuevo-Rosas L, Albero G, Serrano B, Mena M, Gomez D, et al. Human papillomavirus and related diseases report: Japan. Summary report. ICO information centre on HPV and cancer. HPV Information Centre); 2017.

[4] Sakamoto J, Kamiura S, Okayama K, Okodo M, Shibata T, Osaka Y, et al. Single type infection of human papillomavirus as a cause for high-grade cervical intraepithelial neoplasia and invasive cancer in Japan. Papillomavirus Res 2018;6:46–51. https://doi.org/10.1016/j.pvr.2018.10.001.

[5] Wigle J, Fontenot HB, Zimet GD. Global delivery of human papillomavirus vaccines. Pediatr Clin 2016;63:81–95.

[6] Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis 2009;199:805–14.

[7] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11:1048–56.

[8] Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30(Suppl 5):F123–38.

[9] Garland SM, Kjaer SK, Munoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin Infect Dis 2016;63:519–27.

[10] Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015. Pediatr Infect Dis J 2015;34:983–91.

[11] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928–43.

[12] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–27.

[13] Ogawa Y, Takei H, Ogawa R, Mihara K. Safety of human papillomavirus vaccines in healthy young women: a meta-analysis of 24 controlled studies. J Pharm Health Care Sci 2017;3:18.

[14] Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer Sci 2013;104:465–72.

[15] Tanaka H, Shirasawa H, Shimizu D, Sato N, Ooyama N, Takahashi O, et al. Preventive effect of human papillomavirus vaccination on the development of uterine cervical lesions in young Japanese women. J Obstet Gynaecol Res 2017;43:1597–601.

[16] Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res 2009;2:868–78.

[17] Kjaer SK, Nygård M, Dillner J, Munk C, Marshall B, Hansen BT, et al. Long-term effectiveness of the quadrivalent human papillomavirus vaccine in 16- to 23-year-old girls and women in four Nordic countries. Clin Infect Dis 2017. 110.1093/cid/cix797.

[18] Malagón T, Drolet M, Boily MC, Franco EL, Jit M, Brisson J, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:781–9.

[19] Luxembourg A Moeller E. 9-Valent human papillomavirus vaccine: a review of the clinical development program. Expert Rev Vaccines 2017;16:1119–39.

[20] Yagi A, Ueda Y, Egawa-Takata T, Tanaka Y, Nakae R, Morimoto A, et al. Realistic fear of cervical cancer risk in Japan depending on birth year. Hum Vaccine Immunother 2017;13:1700–4.

[21] World Health Organization (WHO). Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec 2017;92:241–68.