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Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study

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ABSTRACT

Background: The quadrivalent (q) human papillomavirus (HPV) vaccine protects against infection and disease related to HPV types 6, 11, 16, and 18. We report efficacy, immunogenicity, and safety of qHPV vaccine in a Phase 3 study in Japanese men.

Methods: In this randomized, double-blind trial (NCT01862874), Japanese men (aged 16–26 years) were randomized in a 1:1 ratio to receive three doses of qHPV vaccine or placebo (Day 1, Month 2, Month 6). The primary efficacy endpoint was the combined incidence of HPV6/11/16/18-related persistent anogenital infection (detected at ≥2 consecutive visits ≥6 months apart), assessed in the per-protocol population of men who received all three vaccinations, and were seronegative at Day 1 and PCR negative from Day 1 to Month 7 to the relevant HPV type. Results are from the interim and final analyses.

Results: In total, 1124 participants were randomized. The vaccine demonstrated 83.3% (95% confidence interval: 24.9, 98.2; $p = 0.007$) and 85.9% (95% confidence interval: 52.7, 97.3; $p < 0.001$) efficacy against HPV6/11/16/18-related persistent infection in the interim and final analyses, respectively. Two cases of HPV6/11/16/18-related external genital lesions (condyloma and PIN 1) were observed in the placebo group and none in the qHPV vaccine group at study end. At Month 7, >97% of participants who received qHPV vaccine seroconverted to each of the vaccine HPV types. Most participants remained seropositive at Month 36, although the seropositivity rate declined between Months 7 and 36. Vaccination-related adverse events were reported in 60.8% and 56.5% of participants in the qHPV vaccine and placebo groups, respectively; most commonly mild to moderate injection-site pain, erythema, and swelling. Injection-site pain and swelling were more common with qHPV vaccine than placebo (each $p < 0.05$).

Conclusions: Results suggest qHPV vaccine is efficacious against HPV6/11/16/18-related persistent infections, immunogenic, and well-tolerated in Japanese men.

Clinical trial registration identifier: NCT01862874.

1. Introduction

The quadrivalent (q) human papillomavirus (HPV) vaccine protects against infection and disease related to HPV6/11/16/18. In addition to preventing approximately 70% of cervical cancer cases attributable to HPV16/18 in women, the vaccine has potential to prevent more than 84% of anal cancers and 75% of anal intraepithelial neoplasia (AIN) Grade 2 and 3 lesions in both genders, and approximately 70% of HPV-positive penile cancers in men, based on global epidemiologic data [1–3]. The qHPV vaccine also has potential to prevent approximately 90% of genital warts cases attributable to HPV6/11 [4]. A large proportion of oropharyngeal cancers (estimated 18.5–22.4%) are also believed to be driven by HPV [5], with the majority of HPV-attributable head and neck cancers caused by HPV16/18 (84.9%) [6].

The HPV vaccine is included in the immunization programs of more than 70 countries, of which at least 11 include boys [7,8]. Including males in HPV vaccination programs has potential to both prevent HPV-related disease in men and contribute to herd immunity by reducing the spread of HPV infection in males and females [9–11]. Approximately 60,000 male cancer cases are attributable to HPV annually, based on 2012 data, including anal, penile, and oropharyngeal cancer [6]. While anal cancer is relatively rare, the incidence is increasing [12], and screening programs for

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HPV-related cancers in men remain limited [10]. In addition, genital warts is the most common viral sexually transmitted disease, with a lifetime risk of 10% in both genders [11]. HPV infection is common in Japanese men: a study of Japanese men attending a sexually transmitted disease clinic reported HPV prevalence of approximately 19% and 22% in oral and urine samples, respectively [13].

In pivotal clinical trials in young women, the qHPV vaccine demonstrated efficacy against HPV6/11/16/18-related persistent infection and disease [14,15]. In men, the qHPV vaccine prevented HPV6/11/16/18-related external genital lesions, AIN, and persistent infection in an international clinical trial [16,17]; however, this study did not include participants from Japan. We report data from the interim and final analyses of a randomized, placebo-controlled, multicenter study of qHPV vaccine in Japanese men aged 16–26 years. The primary objectives were to evaluate efficacy against HPV6/11/16/18-related persistent infection and tolerability in this population.

2. Materials and methods

2.1. Study design and participants

Protocol V501-122 (NCT01862874) was conducted at 24 sites in Japan, in healthy young men aged 16–26 years (N = 1124). Heterosexual men (HM; n = 1004) must have had exclusively female sexual partners and 1–5 lifetime sexual partners at the time of enrollment. Men who have sex with men (MSM; n = 120) must have engaged in either insertive or receptive anal intercourse or oral sex with a male sexual partner within the past year and must have had up to 5 lifetime male and/or female sexual partners at enrollment. Participants refrained from sexual activity for 2 days before scheduled visits that included sample collection. Those with a history of genital warts, or clinically present external genital warts at Day 1, were excluded.

Participants were randomized in a 1:1 ratio to receive qHPV vaccine or placebo via a central integrated web response system, stratified by HM or MSM. All laboratory personnel, the pathology panel, the investigators, site personnel, and participants were blinded to the vaccination group.

The primary efficacy endpoint was the combined incidence of HPV6/11/16/18-related persistent ($\geq$6 months) infection, and the secondary efficacy endpoint was the combined incidence of HPV6/11/16/18-related persistent infection, condyloma acuminata, and penile/perianal/perineal intraepithelial neoplasia (PIN), or penile, perianal, or perineal cancer. The incidence of HPV6/11/16/18-related condyloma acuminata was a pre-specified exploratory objective. Other efficacy endpoints included the combined incidence of HPV6/11/16/18-related intra-anal persistent infection. Tolerability, based on adverse events (AEs), vaccination-related AEs, and new medical conditions, was also assessed as a primary objective, and immunogenicity (seroconversion percentages and geometric mean titers [GMT]) was evaluated as an exploratory endpoint.

The event-driven primary analysis was planned after observation of at least 18 primary efficacy cases. A pre-specified interim analysis was conducted when at least 11 cases were observed and reviewed by the external Data Monitoring Committee, which was formed to conduct interim analysis and make recommendations to the sponsor based on reviewing the interim analysis results. Based on pre-specified criteria, the Data Monitoring Committee could recommend the primary analysis be conducted after accrual of 11 events; otherwise, it was to be conducted after accrual of 18 events. Because significant results for the primary efficacy hypothesis were observed during the interim analysis, unblinding was performed and the primary analysis conducted. After the interim analysis, the study continued and the final study visit was completed at Month 36. We report the results from this interim analysis (database lock: April 24, 2017) and the final analysis (database lock: February 5, 2018).

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies; all participants (or, for minor participants, parent/legal guardian and participant) provided written informed consent.

2.2. Vaccination and follow-up

Vaccine or placebo were administered as 0.5-mL intramuscular injections on Day 1 and at Months 2 and 6. Each dose of the qHPV vaccine contained HPV6/11/16/18 L1 viral-like particles 20/40/40/20 μg, respectively, and 225 μg aluminum (as aluminum hydroxyphosphate sulfate adjuvant). The placebo doses contained the adjuvant alone.

Genitourinary examinations and collection of specimens for HPV polymerase chain reaction (PCR) testing were performed on Day 1 and at Month 7, Month 12, and every 6 months thereafter. Based on genitourinary and perianal inspections, all new (i.e. occurring after Day 1) lesions judged by the investigator to be possibly, probably, or definitely related to HPV or of unknown etiology were biopsied. External genital lesion biopsies were processed and read by a sponsor-designated central laboratory; the central laboratory diagnosis was used for case management purposes. Biopsy tissues were also reviewed by the HPV Vaccine Program Pathology Panel, and the panel consensus diagnosis was used to determine clinical disease efficacy endpoints.

HPV PCR analysis was performed on all external genital lesion specimens using Thinsection microtomy sections. Specimens for HPV (types 6/11/16/18/31/33/35/39/45/51/52/56/58/59) PCR testing were collected from the penis, scrotum, and perianal region using a nail file followed by a wetted DACRON™ swab system, as described previously [16]; an intra-anal sample was also collected for HPV PCR testing. Persistent infection was defined as an HPV type detected in samples from two or more consecutive visits (±1-month visit windows) at least 6 months apart.

For immunogenicity assessments, anti-HPV6/11/16/18 antibodies were detected in serum collected on Day 1 and at Months 7 and 36 by competitive Luminex immunoassay [18].

Participants were observed for at least 30 min after vaccination for any untoward effects, particularly allergic reactions. Information about oral temperature (Days 1–5), injection-site AEs (Days 1–5), systemic AEs, and serious AEs (SAEs) was collected using vaccination report cards for 15 days following each vaccination. Information about vaccination-related SAEs and deaths was collected throughout the study.

2.3. Statistical analysis

The primary efficacy analysis was conducted in the per-protocol efficacy (PPE) population, which included participants who: received all three vaccinations within 1 year; did not have any protocol deviations that could potentially interfere with the vaccine efficacy; had at least one follow-up after Month 7; and were seronegative at Day 1 and PCR negative from Day 1 through Month 7 to HPV6/11/16/18. Supportive analyses were conducted in the full analysis set (FAS) and naïve to the relevant HPV type (HNRT) populations, with cases counted starting after Day 1. The FAS included all participants who received at least one vaccination and had any follow-up visit, regardless of HPV status at baseline. The HNRT population included those participants who received at least one vaccination and had any follow-up visit who were seronegative and PCR negative at Day 1 to the relevant HPV type.

The secondary efficacy analyses were conducted in the PPE population for all participants and also for subgroups of HM and MSM participants.

The primary efficacy hypothesis was tested using a one-sided exact test, based on a binomial distribution that conditions on the total number of cases. Vaccine efficacy was defined as $(1 - R_{qHPV}/R_{placebo}) \times 100$ [%], where R_{qHPV} and $R_{placebo}$ are incidence of persistent infection with qHPV vaccine and placebo, respectively.

Immunogenicity was assessed in the per-protocol immunogenicity population of participants who: received all three vaccinations within acceptable day ranges; provided blood samples for serology testing within an acceptable day range; did not have any major protocol violations; and were seronegative at Day 1 and PCR negative from Day 1 through Month 7 for the appropriate HPV types. HPV6/11/16/18-seroconversion percentages and GMT at Months 7 and 36 were evaluated by computing point estimates and constructing 95% confidence intervals (CIs) for all participants, and for HM and MSM subgroups.

Safety was assessed in all participants who received at least one vaccination and had follow-up data. AEs were summarized as frequencies and percentages by vaccination group, by vaccination visit, and across all vaccination visits. For vaccination report card-recorded injection-site AEs and temperature elevations ($\geq$37.5 °C), across all vaccination visits, treatment differences (incidence qHPV vaccine–placebo) and 95% CIs were calculated using the Miettinen and Nurminen method.

The planned enrollment of 1100 participants was based on observed incidence rates of HPV6/11/16/18-related persistent infection in Asian men who received placebo in a global study of qHPV vaccine [16]. Based on an estimated incidence rate of HPV6/11/16/18-related persistent infection of 2.3 per 100 person-years, and assuming a vaccine efficacy of 85%, approximately 59% of enrolled participants would have evaluable data, and one interim analysis when 11 persistent infection cases were observed, the study has at least 90% power to achieve success for the primary hypothesis. The statistical criterion for success is based on the lower bound of the two-sided CI for vaccine efficacy being >0. The alpha boundary ($\alpha = 0.0113$) for the interim analysis was determined based on the Hwang-Shih-Decani alpha spending function ($\gamma = -3.4$) with the actual number of events observed up to the interim analysis. The trial had >56% power to detect significant vaccine efficacy if the true vaccine efficacy is 85%.

3. Results

3.1. Participants

Beginning on June 28, 2013, 1124 participants were randomized, 1123 received at least one vaccination, and 1062 completed all three vaccinations (Fig. 1). A total of 61 participants (n = 31 qHPV vaccine; 30 placebo) discontinued from the trial before receiving all three vaccinations, most commonly due to loss to follow-up or withdrawal by participant. An additional 94 participants (n = 47, qHPV vaccine group; n = 47, placebo group) discontinued between Months 6 and 36. Baseline characteristics were well balanced across vaccination groups (Table 1). The mean age in both groups was 22.6 years, and 89.3% of participants were HM in each group.

3.2. Efficacy against HPV6/11/16/18-related persistent infection and disease

3.2.1. Interim analysis

In the PPE population, there were 12 cases of HPV6/11/16/18-related persistent infection (primary endpoint) in the placebo group compared with two in the qHPV vaccine group (vaccine efficacy: 83.3% [95% CI: 24.9, 98.2], $p = 0.007$) (Table 2). Of the two cases of HPV6/11/16/18-related persistent infection observed in the qHPV vaccine group, one was HPV6 related and one HPV16 related. Among subgroups of HM and MSM, efficacy was 77.3% (95% CI: −9.8, 97.6; qHPV: 2 cases; placebo: 9 cases) and 100% (95% CI: −107.9, 100; qHPV: 0 cases; placebo: 3 cases), respectively. No cases of HPV6/11/16/18-related external genital lesions were observed in the qHPV vaccine or placebo groups (Table 2). Thus, efficacy against the combined incidence of HPV6/11/16/18-related persistent infection and external genital lesions was 83.4% (95% CI: 25.6, 98.2), similar to efficacy against the endpoint of persistent infection only (Table 2).

In the PPE population, there were four cases of HPV6/11/16/18-related intra-anal persistent infection in the placebo group compared with none in the qHPV vaccine group (vaccine efficacy: 100% [95% CI: −51.2, 100]). Similarly, among subgroups of HM and MSM, efficacy was 100% (95% CI: −442.6, 100; qHPV: 0 cases; placebo: 2 cases) and 100% (95% CI: −344.9, 100; qHPV: 0 cases; placebo: 2 cases), respectively (Table 3).

In supportive analyses conducted in the HNRT population, efficacy against HPV6/11/16/18-related persistent infection was 88.8% (95% CI: 53.4, 98.7; qHPV: 2 cases; placebo: 18 cases) (Supplementary material, Table 1). In the FAS, which included participants who were infected with vaccine HPV types at baseline, efficacy against HPV6/11/16/18-related persistent infection was 55.4% (95% CI: 9.0, 79.4; qHPV: 12 cases; placebo: 27 cases) (Supplementary material, Table 2).

3.2.2. Final analysis

At the end of the study, there were an additional nine cases and one case of HPV6/11/16/18-related persistent infection in the placebo and qHPV vaccine groups, respectively, in the PPE population. The efficacy against the incidence of HPV6/11/16/18-related persistent infection was 85.9% (95% CI: 52.7, 97.3; $p < 0.001$), similar to that observed in the interim analysis without attenuation (Table 2). Among subgroups of HM and MSM, efficacy was 87.4% (95% CI: 46.3, 98.6; qHPV: 2 cases; placebo: 16 cases over the entire study) and 83.6% (95% CI: −46.4, 99.7 qHPV: 1 case; placebo: 5 cases), respectively. There were no cases of HPV6/11/16/18-related external genital lesions in the qHPV vaccine group. Two cases of HPV6/11/16/18-related external genital lesions were observed in the placebo group: one case each of condyloma and PIN 1. Thus, the efficacy against the combined incidence of HPV6/11/16/18-related persistent infection and external genital lesions was 86.5% (95% CI: 55.2, 97.4; $p < 0.001$) (Table 2).

In the PPE population, there were nine cases of HPV6/11/16/18-related intra-anal persistent infection in the placebo group compared with none in the qHPV vaccine group (vaccine efficacy: 100% [95% CI: 49.3, 100]). Similarly, among subgroups of HM and MSM, efficacy was 100% (95% CI: 13.4, 100; qHPV: 0 cases; placebo: 6 cases) and 100% (95% CI: −105.9, 100; qHPV: 0 cases; placebo: 3 cases), respectively (Table 3).

In supportive analyses conducted in the HNRT population, efficacy against HPV6/11/16/18-related persistent infection was 85.4% (95% CI: 58.2, 96.3; qHPV: 4 cases; placebo: 27 cases) (Supplementary material, Table 1). In the FAS, which included participants who were infected with vaccine HPV types at baseline, efficacy against HPV6/11/16/18-related persistent infection was 61.8% (95% CI: 27.4, 81.0; qHPV: 14 cases; placebo: 36 cases) (Supplementary material, Table 2).

3.3. Immunogenicity

At Month 7 (1 month after the last vaccination), seroconversion for HPV 6, 11, 16, and 18 occurred in 97.1–100% of participants who

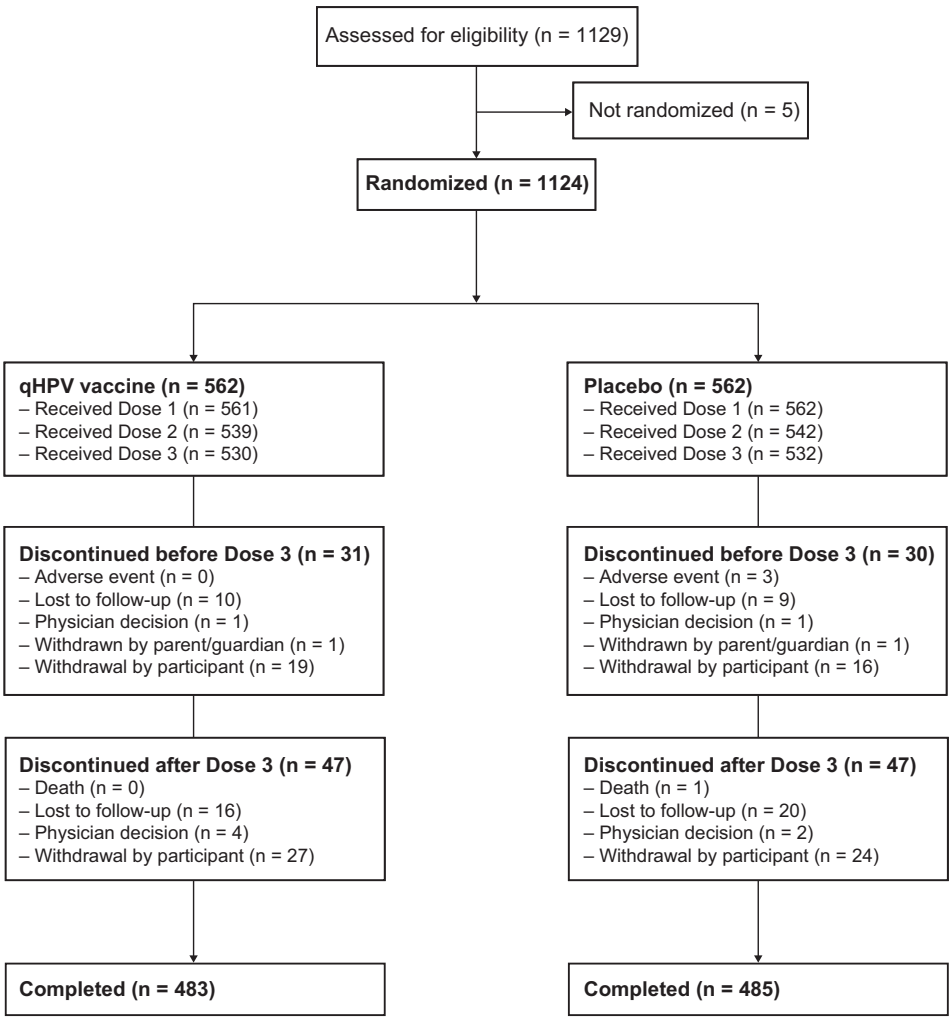

Fig. 1. Participant disposition. qHPV, quadrivalent human papillomavirus.

Table 1
Participant characteristics by vaccination group (all randomized participants).

	qHPV vaccine (N = 562)	Placebo (N = 562)
Age		
Mean (SD)	22.6 (2.1)	22.6 (2.0)
Median (range)	22.0 (18–27)	22.0 (17–26)
Smoking status, n (%)		
Current	210 (37.4)	201 (35.8)
Former	62 (11.0)	55 (9.8)
Never	290 (51.6)	306 (54.4)
Sexual orientation, n (%)		
HM	502 (89.3)	502 (89.3)
MSM	60 (10.7)	60 (10.7)
Lifetime sexual partners, n (%)		
0	1 (0.2)	1 (0.2)
1 to 4	467 (83.1)	467 (83.1)
>4	94 (16.7)	94 (16.7)

HM, heterosexual men; MSM, men who have sex with men; qHPV, quadrivalent human papillomavirus; SD, standard deviation.

received the qHPV vaccine (Table 4). Anti-HPV antibody GMTs were 384.1, 458.3, 2264.4, and 365.2 milli-Merck units (mMU)/mL for HPV 6, 11, 16, and 18, respectively, at Month 7 (Table 4). GMTs were generally higher in the HM subgroup compared with the MSM subgroup at Month 7 (Supplementary material, Table 3). At the end of the study (Month 36), 60.7–92.3% of participants who received the qHPV vaccine remained seropositive to HPV 6, 11, 16, and 18, respectively (Table 4). Anti-HPV antibody GMTs were 67.5, 42.9, 203.0, and 32.6 mMU/mL for HPV 6, 11, 16, and 18, respectively, at Month 36 (Table 4). Similar to the Month 7 analysis, GMTs were generally higher in the HM subgroup compared with the MSM subgroup at Month 36 (Supplementary material, Table 3).

3.4. Safety

The incidence of AEs and vaccination-related AEs was generally similar between the qHPV vaccine and placebo groups (Table 5). The incidence of overall and vaccination-related AEs within 15 days following any vaccination was 63.9% (n = 354) and 60.8% (n = 337) in the qHPV group, respectively, and 59.9% (n = 335) and 56.5% (n = 316) in the placebo group, respectively (Table 5).

Vaccination-related injection-site AEs were reported in 59.6% (n = 330) and 55.1% (n = 308) of qHPV vaccine and placebo recipients, respectively; the most common were injection-site pain, erythema, and swelling (Table 5). Injection-site pain and swelling were more common with qHPV vaccine than placebo (each $p < 0.05$; Supplementary material, Table 4). The majority of injection-site AEs were mild or moderate in intensity and transient (i.e. most cases resolved within 1 week).

Systemic AEs were reported in 14.4% of qHPV vaccine and 15.4% of placebo recipients; of those, 3.4% and 5.0% of participants, respectively, experienced systemic AEs that were considered vac-

Table 2
Efficacy against HPV6/11/16/18-related persistent infection and external genital disease (PPE population).

Endpoint	qHPV vaccine (N = 561)				Placebo (N = 562)				Observed efficacy (%)	95% CI
	n	No. of cases	Person-years at risk	Incidence rate per 100 person-years at risk	n	No. of cases	Person-years at risk	Incidence rate per 100 person-years at risk		
Interim analysis										
HPV6/11/16/18-related persistent infection	494	2	730.4	0.3	494	12	733.0	1.6	83.3	24.9, 98.2
By HPV type										
HPV6	476	1	705.2	0.1	465	4	693.7	0.6	75.4	−148.5, 99.5
HPV11	476	0	706.1	0.0	465	3	694.2	0.4	100	−137.9, 100
HPV16	469	1	694.0	0.1	468	3	699.2	0.4	66.4	−318.3, 99.4
HPV18	491	0	729.1	0.0	481	3	718.0	0.4	100	−138.3, 100
By sexual orientation										
HM	438	2	646.7	0.3	443	9	661.1	1.4	77.3	−9.8, 97.6
MSM	56	0	83.7	0.0	51	3	71.9	4.2	100	−107.9, 100
HPV6/11/16/18-related persistent infection and disease	498	2	751.6	0.3	498	12	747.4	1.6	83.4	25.6, 98.2
By persistent infection or disease										
HPV6/11/16/18-related persistent infection	494	2	730.4	0.3	494	12	733.0	1.6	83.3	24.9, 98.2
HPV6/11/16/18-related disease	498	0	754.1	0.0	498	0	754.8	0.0	NA	NA
Final analysis										
HPV6/11/16/18-related persistent infection	497	3	1136.8	0.3	498	21	1123.2	1.9	85.9	52.7, 97.3
By HPV type										
HPV6	479	1	1099.9	0.1	469	7	1074.0	0.7	86.1	−8.6, 99.7
HPV11	479	0	1101.9	0.0	469	3	1078.8	0.3	100	−136.9, 100
HPV16	472	2	1080.8	0.2	472	7	1080.4	0.6	71.4	−50.0, 97.1
HPV18	494	0	1136.9	0.0	485	5	1110.0	0.5	100	−6.5, 100
By sexual orientation										
HM	441	2	1008.6	0.2	447	16	1018.2	1.6	87.4	46.3, 98.6
MSM	56	1	128.2	0.8	51	5	105.0	4.8	83.6	−46.4, 99.7
HPV6/11/16/18-related persistent infection and disease	498	3	1147.5	0.3	498	22	1132.0	1.9	86.5	55.2, 97.4
By persistent infection or disease										
HPV6/11/16/18-related persistent infection	497	3	1136.8	0.3	498	21	1123.2	1.9	85.9	52.7, 97.3
HPV6/11/16/18-related disease	498	0	1152.4	0.0	498	2	1157.5	0.2	100	−434.8, 100

CI, confidence interval; HM, heterosexual men; HPV, human papillomavirus; MSM, men who have sex with men; N = number of participants randomized to the respective vaccination group who received at least one injection; n = number of participants evaluable (i.e. number of participants in the given population who also have at least one follow-up visit after Month 7); PPE, per-protocol efficacy; qHPV, quadrivalent human papillomavirus.

cine related (Table 5). The frequencies of individual systemic AEs and vaccine-related systemic AEs were similar with qHPV vaccine and placebo. The most common vaccine-related systemic AEs were pyrexia (qHPV: 1.4%; placebo: 1.6%) and headache (qHPV: 0.4%; placebo: 1.3%).

No SAEs were reported within 15 days of any vaccination (Table 5). However, one participant in the placebo group died on Day 440 after completion of the three-dose regimen (suicide); this death was not considered vaccine related. No other SAEs were reported over the entire study period.

Three participants (all in the placebo group) discontinued vaccination due to AEs within 15 days following a vaccination: one due to bronchospasm (mild) on Day 4 following Vaccination 1 (resolved after 17 days [2.43 weeks]); one due to bronchitis (moderate) on Day 1 following Vaccination 1 (resolved at Week 1); and one due to injection-site erosion (moderate) on Day 4 following Vaccination 1 (resolved at Week 2). These events were considered by the investigator to be vaccine related.

4. Discussion

In the interim analysis, the qHPV vaccine demonstrated robust efficacy (83.3%) against HPV6/11/16/18-related persistent (≥6 months) infection in young Japanese men. There were no cases of external genital lesions in either the vaccine or placebo group during the interim analysis. Therefore, efficacy against the combined endpoint of HPV6/11/16/18-related persistent infection and disease (83.4%) was nearly identical to that observed against persistent infection alone. The efficacy observed at the time of the interim analysis continued without attenuation through Month 36 (85.9% efficacy against HPV6/11/16/18-related persistent infection at end of study). After the interim analysis, there were two cases of external genital lesions in the placebo group and none in the qHPV vaccine group.

The observed qHPV vaccine efficacy against the collective incidence of HPV6/11/16/18-related persistent infection among Japanese men is consistent with results from a prior international

Table 3
Efficacy against HPV6/11/16/18-related intra-anal persistent infection (PPE population).

Endpoint	qHPV vaccine (N = 561)				Placebo (N = 562)				Observed efficacy (%)	95% CI
	n	No. of cases	Person-years at risk	Incidence rate per 100 person-years at risk	n	No. of cases	Person-years at risk	Incidence rate per 100 person-years at risk		
Interim analysis										
HPV6/11/16/18-related intra-anal persistent infection	491	0	722.3	0.0	495	4	720.8	0.6	100	−51.2, 100
By HPV type										
HPV6	473	0	695.5	0.0	466	2	678.4	0.3	100	−419.3, 100
HPV11	473	0	695.5	0.0	466	2	678.5	0.3	100	−419.4, 100
HPV16	466	0	684.9	0.0	469	0	683.9	0.0	NA	NA
HPV18	488	0	718.5	0.0	482	1	704.6	0.1	100	−3724.8, 100
By sexual orientation										
HM	435	0	639.1	0.0	445	2	651.2	0.3	100	−442.6, 100
MSM	56	0	83.2	0.0	50	2	69.5	2.9	100	−344.9, 100
Final analysis										
HPV6/11/16/18-related intra-anal persistent infection	494	0	1116.6	0.0	498	9	1116.6	0.8	100	49.3, 100
By HPV type										
HPV6	476	0	1077.9	0.0	469	2	1058.3	0.2	100	−422.8, 100
HPV11	476	0	1077.9	0.0	469	3	1058.4	0.3	100	−137.6, 100
HPV16	469	0	1059.6	0.0	472	2	1063.1	0.2	100	−434.3, 100
HPV18	491	0	1111.7	0.0	485	3	1091.1	0.3	100	−137.5, 100
By sexual orientation										
HM	438	0	989.4	0.0	447	6	1008.4	0.6	100	13.4, 100
MSM	56	0	127.1	0.0	51	3	108.2	2.8	100	− 105.9, 100

CI, confidence interval; HM, heterosexual men; HPV, human papillomavirus; MSM, men who have sex with men; N = number of participants randomized to the respective vaccination group who received at least one injection; n = number of participants evaluable (i.e. number of participants in the given population who also have at least one follow-up visit after Month 7); qHPV, quadrivalent human papillomavirus; PPE, per-protocol efficacy.

clinical trial in young men that did not include Japanese participants [16]. In that study, efficacy against persistent HPV6/11/16/18-related persistent infection was 85.6% compared with placebo in the PPE population [16]. High efficacy against HPV6/11/16/18-related external genital lesions (90.4%) and AIN of any grade (77.5%) or high grade (74.9%) was also observed in the international study [16,17]. Moreover, in an extension study with up to 10 years of follow-up, durable protection from vaccine HPV-type–related genital warts, external genital lesions, and AIN plus sustained immunogenicity were reported [19].

In this study, detailed anal inspection was not conducted and, therefore, no cases of anal lesions were observed. However, intra-anal swab samples were collected from all participants, including HM and MSM participants. Although efficacy against intra-anal HPV infection in MSM was evaluated in a prior international clinical trial [17], this is the first clinical study to our knowledge to evaluate the efficacy of qHPV vaccine against intra-anal HPV infection in HM. The incidence rate of intra-anal persistent infection in HM was observed to be lower than in MSM. Similar to the international trial [17], this study demonstrated robust efficacy of the qHPV vaccine against intra-anal persistent infection in the overall population and in the MSM and HM populations.

The qHPV vaccine elicited strong immune responses, with seroconversion to each HPV type observed in the vast majority (>97%) of participants at 1 month after the third vaccination, and efficacy was maintained at Month 36. These results were consistent with the robust immune responses observed in the prior international study in young men [20]. Similar to the international study, GMTs were somewhat lower among MSM compared with HM [20]. However, the differences in GMTs do not appear to be clinically relevant, as high efficacy of qHPV vaccine has been demonstrated across a wide range of antibody levels [20].

The vaccine was generally well tolerated, with no SAEs reported within 15 days of any vaccination. Consistent with the established safety profile of the qHPV vaccine [7,21], injection-site reactions were the most common AEs. Injection-site AEs were reported by similar proportions of Japanese men in the current study (qHPV: 59.7%; placebo: 55.3%) as previously by international male clinical trial participants (qHPV: 60.1%; placebo: 53.7%) [16]. The incidence of systemic AEs appeared to be lower in this study (qHPV: 14.4%; placebo: 15.4%) than in the international study (qHPV: 31.6%; placebo: 31.4%). No serious vaccine-related AEs were reported here or in the prior international study [16,22], including in a long-term extension with up to 10 years of follow-up [19].

While HPV vaccines with public aid became available to girls in Japan in 2010, the active recommendation for HPV vaccine in Japan was suspended in 2013 due to the occurrence of suspected AEs after vaccination, leading to a sharp decline in the newly vaccinated rate [23–25]. However, no causal association between HPV vaccines and suspected AEs is suggested, based on the results of a recent survey study of >29,000 female residents of Nagoya City [24]. Global studies, including long-term safety in clinical trials and real-world findings in regions where the vaccine has been introduced over the past 10 years, support a favorable safety profile [7,16,21]. The World Health Organization Global Advisory Committee on Vaccine Safety has concluded that the available evidence does not indicate any safety concerns to date that would alter the World Health Organization recommendations for use of the qHPV vaccine [7,23]. Findings from this study further support implementation of widespread vaccination in Japan.

The present findings should be considered in the context of limitations related to sample size and study duration. This study does not have sufficient power to evaluate the disease endpoint (condyloma, PIN, AIN). There were only two cases of

Table 4
Summary of anti-HPV seroconversion rates and GMTs (PPI population).

Assay (cLIA)	qHPV vaccine (N = 561)			Placebo (N = 562)		
	n	GMT[a] (mMU/mL)	95% CI[a]	n	GMT[a] (mMU/mL)	95% CI[a]
Anti-HPV6						
Day 1	436	<7	<7, <7	426	<7	<7, <7
Month 7	436	384.1	361.8, 407.8	426	<7	<7, <7
Month 36	436	67.5	62.0, 73.5	426	<7	<7, <7
Anti-HPV11						
Day 1	436	<8	<8, <8	426	<8	<8, <8
Month 7	436	458.3	432.9, 485.2	426	<8	<8, <8
Month 36	436	42.9	39.0, 47.1	426	<8	<8, <8
Anti-HPV16						
Day 1	428	<11	<11, <11	429	<11	<11, <11
Month 7	428	2264.4	2126.5, 2411.2	429	<11	<11, <11
Month 36	428	203.0	182.1, 226.4	429	<11	<11, <11
Anti-HPV18						
Day 1	450	<10	<10, <10	441	<10	<10, <10
Month 7	450	365.2	335.7, 397.3	441	<10	<10, <10
Month 36	450	32.6	29.7, 35.8	441	<10	<10, <10
Seroconversion	**n**	**Percent[b]**	**95% CI**	**n**	**Percent[b]**	**95% CI**
HPV6 (cLIA ≥ 20mMU/mL)						
Day 1	436	0.0	0.0, 0.8	426	0.0	0.0, 0.9
Month 7	436	99.3	98.0, 99.9	426	0.2	0.0, 1.3
Month 36	436	86.9	83.4, 89.9	426	5.6	3.6, 8.3
HPV11 (cLIA ≥ 16mMU/mL)						
Day 1	436	0.0	0.0, 0.8	426	0.0	0.0, 0.9
Month 7	436	99.8	98.7, 100	426	0.2	0.0, 1.3
Month 36	436	78.0	73.8, 81.8	426	5.4	3.5, 8.0
HPV16 (cLIA ≥ 20mMU/mL)						
Day 1	428	0.0	0.0, 0.9	429	0.0	0.0, 0.9
Month 7	428	100	99.1, 100	429	0.2	0.0, 1.3
Month 36	428	92.3	89.3, 94.6	429	4.4	2.7, 6.8
HPV18 (cLIA ≥ 24mMU/mL)						
Day 1	450	0.0	0.0, 0.8	441	0.0	0.0, 0.8
Month 7	450	97.1	95.1, 98.5	441	1.1	0.4, 2.6
Month 36	450	60.7	56.0, 65.2	441	2.9	1.6, 5.0

ANOVA, analysis of variance; CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HPV, human papillomavirus; mMU, milli-Merck units; N = number of participants randomized to the respective vaccination group who received at least one injection; n = number of participants contributing to the analysis; PPI, per-protocol immunogenicity; qHPV, quadrivalent human papillomavirus.
[a] The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group on the log-scale.
[b] Seroconversion percentage calculated as 100*number of participants with indicated response/number of participants contributing to the analysis.

Table 5
AE summary among all vaccinated participants (Days 1–15 following any vaccination visit).

n (%)	qHPV vaccine (N = 554)	Placebo (N = 559)
Any AE	354 (63.9)	335 (59.9)
Injection-site AEs	331 (59.7)	309 (55.3)
Systemic AEs	80 (14.4)	86 (15.4)
Vaccination-related AE	337 (60.8)	316 (56.5)
Injection-site AEs	330 (59.6)	308 (55.1)
Systemic AEs	19 (3.4)	28 (5.0)
SAE	0	0
Death	0	0
Discontinued due to AE	0	3 (0.5)
Discontinued due to vaccination-related AE	0	3 (0.5)
Most common vaccination-related AEs (>1%)		
Injection-site pain[a]	303 (54.7)	271 (48.5)
Injection-site erythema[a]	136 (24.5)	121 (21.6)
Injection-site swelling[a]	118 (21.3)	81 (14.5)
Injection-site pruritus[a]	6 (1.1)	4 (0.7)
Pyrexia[b]	8 (1.4)	9 (1.6)
Headache	2 (0.4)	7 (1.3)

AE, adverse event; qHPV, quadrivalent human papillomavirus; SAE, serious adverse event.
[a] Days 1–5 following any vaccination.
[b] Pyrexia was defined as ≥37.5 °C.

HPV6/11/16/18-related anogenital disease at the final analysis. However, vaccine efficacy against HPV-related disease in Japanese men is expected, as the efficacy against persistent infection and immunogenicity were similar to the international study in men that did not include Japan [16,17].

Currently in Japan, the female HPV vaccination rate is extremely low [26]. If this trend of low vaccination rates in Japanese girls continues, the inclusion of males in vaccination programs will become more important for the prevention of HPV-related diseases. Gender-neutral vaccination is expected to be most cost-effective in cases where HPV vaccination coverage in girls is below 50% [7].

4.1. Conclusions

In this study, the qHPV vaccine demonstrated efficacy against vaccine-type–related persistent infection, elicited robust immune responses, and was not associated with any new safety signals in young Japanese men.

Conflict of interest

HM and YY have nothing to disclose. SM, RY, SRH, AW, MS, and YT are employees of MSD K.K., Tokyo, Japan.

Author contributions

All authors attest they meet the ICMJE criteria for authorship. SM, RY, SRH, AW, MS, and YT contributed to conception, design, or planning the study; YY and SRH contributed to data analysis; RY acquired data; HM, SM, RY, AW, MS, and YT interpreted the results. All authors critically reviewed or revised the manuscript for important intellectual content, reviewed the final version of the manuscript and agreed with its content and submission.

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Appendix A. Supplementary material

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