Original Article

Safety and Immunogenicity of the Quadrivalent HPV Vaccine in Japanese Boys: a Phase 3, Open-Label Study

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SUMMARY: Human papillomavirus (HPV)-associated disease is common among men with HPV infection. A quadrivalent HPV (qHPV) vaccine has demonstrated 85.9% efficacy against HPV6/11/16/18-related, persistent (> 6 month) infection in a study of Japanese men aged 16–26 years old. Here, we report the results of an open-label study of the immunogenicity and tolerability of the qHPV vaccine (NCT02576054), conducted to bridge findings from Japanese men to Japanese boys aged 9–15 years old. A total of 100 boys completed a three-vaccination regimen (Day 1, and Months 2 and 6), and 99 boys were included in the primary analysis population. The rate of seroconversion at one month after vaccine Dose 3 (Month 7) was high for each type of HPV (anti-HPV6/11/16/18 geometric mean titers were 482.9 mMU/mL, 1052.8 mMU/mL, 3878.3 mMU/mL, and 1114.5 mMU/mL, respectively. Immune responses to the qHPV vaccine were non-inferior among Japanese boys included in the current study and compared with young Japanese men from a separate study. Injection-site reactions were the most common adverse events, and administration of the vaccine was well tolerated in Japanese boys.

INTRODUCTION

Human papillomavirus (HPV) infection causes benign and malignant diseases, localized primarily in the anogenital area and in the aerodigestive tract, in both genders (1). Besides causing the majority of cervical cancers, HPV infection has an association with the development of genital warts and other cancers, including anal, oropharyngeal, and penile cancer (2–4). Indeed, HPV is responsible for approximately 4.5% of cancers worldwide (630,000 new cases/year: 570,000 in females and 60,000 in males), based on global epidemiology data from 2012 (5). An estimated 16,000 of these HPV-related cancers occurred in Japan and in the Republic of Korea (5). While anal cancer is rare, its incidence has risen, with the majority of anal cancers and approximately 30–42% of penile cancers caused by HPV (3, 6). HPV is also associated with approximately 18.5–22.4% of oropharyngeal cancers (7), and oral HPV infection is common among sexually-active Japanese men (8). Genital warts, which is associated with HPV/11 infections, is the most common sexually-transmitted viral disease, with a lifetime risk of 10% in both genders (9). Despite this, there remains a lack of healthcare programs tackling HPV-related cancers in men (10).

GARDASIL™ is a quadrivalent HPV (qHPV) vaccine (Merck & Co. Inc., Kenilworth, NJ, USA) that is approved in > 130 countries, for use from age 9, for the prevention of premalignant genital lesions (cervical, vulvar, and vaginal), premalignant anal lesions, cervical cancers, anal cancers causally related to certain oncogenic HPV types, and genital warts (condyloma acuminata) causally related to specific HPV types. Prophylactic HPV vaccination can potentially reduce the burden of HPV-associated diseases, including preventing 70% of cervical cancers attributable to HPV16/18 in women (3,11) and 90% of genital warts cases attributable to HPV6/11 in both genders (12).

The prophylactic efficacy of the qHPV vaccine against HPV6/11/16/18-related lesions has been shown in clinical trials in young women, demonstrating high immunogenicity and efficacy against HPV6/11/16/18-related persistent infection and disease (13,14). In an international clinical trial in males, the qHPV vaccine prevented HPV6/11/16/18-related external genital lesions, anal intraepithelial neoplasia, and persistent infection; however, this study did not include participants from Japan (15,16). Based on these data, the qHPV vaccine has been approved in males for the prevention of HPV-related genital warts and anal cancer and/or precancers in > 70 countries worldwide (excluding Japan). In a separate clinical trial, the efficacy of the qHPV vaccine in young Japanese men (aged 16–26 years old) was 85.9% against HPV6/11/16/18-related persistent (> 6 months) infection (NCT01862874).

Male vaccination not only prevents HPV-related diseases in men, but may contribute to herd immunity (9,17), which can potentially reduce the spread of HPV infection in both genders. Due to the prophylactic nature...
of the qHPV vaccine, it would be most effective when administered before HPV exposure through sexual contact. Females have the highest risk of acquiring HPV infection in the 2–5 years old between menarche and sexual debut (18); therefore, data from a young, sexually-inactive population are needed. International studies in male and female adolescents (aged 9–15 years old) showed that the qHPV vaccine is generally well-tolerated (19,20) and produced higher anti-HPV responses (19) in adolescents than in young adult women (aged 16–23 years old) (19).

Here, we describe data from a non-randomized, multi-site, open-label study of the immunogenicity, safety, and tolerability of the qHPV vaccine in healthy Japanese boys. To our knowledge, this is the first study to assess the effects of the qHPV vaccine in young Japanese boys (aged < 16 years old). This study was designed to bridge the qHPV vaccine efficacy findings from the international (15,16) and Japanese clinical trials in young adult men and allow for the comparison of the immunogenicity against HPV6/11/16/18 in Japanese boys versus young adult men enrolled in a separate Japanese clinical trial.

MATERIALS AND METHODS

Study design and participants: Study V501-200 (NCT02576054) is a non-randomized, open-label, single-arm clinical trial of the immunogenicity and tolerability of the qHPV vaccine in healthy Japanese boys, conducted at four sites in Japan. The study was performed between September 2015 (when the first participant signed the informed consent) and January 2019 (when the sponsor received the last assay results [e.g., serum] or participant data from the last study-related phone call/visit). The study consisted of two periods (Fig. 1). Period 1 evaluated the immunogenicity and tolerability of the qHPV vaccine from the first participant visit (Day 1) to the fourth participant visit (Month 7), and one month after the last day of vaccination (21 November 2015 to 3 October 2016). Period 2 evaluated the long-term immunogenicity and safety of the qHPV vaccine from the first participant visit (Day 1) to the last participant visit (Month 30; ongoing). Here, we report the results from Period 1.

Participants were healthy 9–15-years-old Japanese boys with a legal representative who fully understood study procedures, alternative treatments available, the risks involved with the study, provided written informed consent for the trial on behalf of the participant, and could also read, understand, and complete the vaccination report card (VRC). Participants had not yet had sexual intercourse or did not plan on becoming sexually active from Day 1 and until Month 7 of the study, and did not have an oral temperature of ≥ 37.5°C during the 24 hours prior to vaccinations (if this occurred, the Day 1 visit was rescheduled for a time when this criterion could be met). Boys with a history of prior HPV vaccination or with plans to receive the HPV vaccine outside of the study were excluded, as were boys with a history of genital warts or a positive test for HPV. Review of prior medications was performed by the investigator/qualified designee and documented in the data collection system, along with any concomitant medications.

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent from their parent/legal guardian.

Study endpoints: The primary immunogenicity objective was to demonstrate that administration of the qHPV vaccine induces high seroconversion rates for the various HPV types (6,11,16, and 18) at one month after vaccine Dose 3 (Month 7). Seroconversion was defined as a change in serostatus, from seronegative to seropositive. A participant with a competitive Luminex Immunoassay (cLIA) titer at or above the serostatus cutoff for a given HPV type was considered seropositive for that HPV type.

A secondary objective was to estimate cLIA geometric mean titers (GMTs) for HPV6/11/16/18 at one month after vaccine Dose 3. This study was designed to bridge the qHPV vaccine efficacy findings in young adult men in an overseas clinical trial (NCT00090285) and a clinical trial in Japanese men (NCT01862874) to Japanese boys. A secondary objective of this study was to demonstrate that the administration of
qHPV vaccine induces non-inferior GMTs for serum anti-HPV 6/11/16/18 at one month after vaccine Dose 3 in 9–15-years-old Japanese boys compared with 16–26-years-old Japanese men enrolled in NCT01862874. Moreover, describing the persistence of serum antibody titers for vaccine HPV types 24 months after vaccine Dose 3 is a prospective objective of this study (data not yet available).

Vaccine tolerability was assessed as a primary objective. Safety and tolerability were assessed by clinical review of the following parameters: overall, vaccine-related injection-site (Days 1–5), and systemic adverse events (AEs; Days 1–15), as reported on VRCs; serious AEs (SAEs; Days 1–15); vaccine-related SAEs (throughout the study); and new medical conditions (throughout the study). The specific events of interest were injection-site AEs prompted by the VRC, such as pain/tenderness, swelling, and erythema occurring from Days 1–5 following any vaccination, and elevated temperature (≥ 37.5°C) from Days 1–5 following any vaccination.

**Vaccination and follow-up:** The qHPV vaccine was administered as an intramuscular injection of 0.5 mL at Day 1, Month 2, and Month 6, and each dose contained 20 µg HPV6, 40 µg HPV11, 40 µg HPV16, and 20 µg HPV18 L1 VLP, and 225 µg aluminum hydroxyphosphate sulfate adjuvant. All participants were observed for at least 30 min after each vaccination for any untoward effects, including allergic reactions. Immunogenicity was assessed at Day 1 and Month 7. The qHPV cLIA was the primary assay used for the primary and secondary endpoints of the trial. For each visit that required a serum specimen for anti-HPV measurements, a blood specimen of 10 mL was collected in a non-heparinized, non-serum separator, red-top tube, and separated to avoid hemolysis.

**Statistical analyses:** The per-protocol immunogenicity (PPI) population was the primary population for analysis of the immune response to HPV6/11/16/18. To be included in the PPI populations, the participants had to have received all three vaccinations with the correct dose of the correct clinical material, with each vaccination visit occurring within an acceptable range of days. The participants had to have provided a Month 7 serology result within 21–49 days post-Dose 3 and had to be seronegative for the appropriate HPV type at Day 1. To be included in the PPI population for HPV types 6 and 11, the participants had to be seronegative to HPV6/11 at Day 1. For any other vaccine HPV type, the participants had to be seronegative at Day 1 only for the HPV type being analyzed.

Positive serology was defined as having a titer at or above the serostatus cut-off (20 milli-Merck units/mL [mMU/mL], 16 mMU/mL, 20 mMU/mL, and 24 mMU/mL for HPV6/11/16/18 types, respectively). The serostatus positive rate (i.e., seropositivity rate) was the percentage of participants who received vaccination and had a positive titer for the HPV types. In the PPI population, the serostatus of the participants for the relevant HPV types at Day 1 was negative (seropositivity rate = 0%). Seroconversion was defined as a change in the serostatus from seronegative to seropositive. The point estimate and 95% confidence intervals (CIs) were provided for the seroconversion rate for each HPV type.

Anti-HPV6/11/16/18 seroconversion percentages and GMTs at Month 7 were evaluated by computing point estimates and constructing 95% CIs. The GMTs were natural log-transformed before analysis. As such, the CIs for the means were constructed on the natural-log scale and referenced the t-distribution. Exponentiating the means, and lower and upper limits of these CIs yielded estimates for the population GMT and CIs about the GMT on the original scale. Immune responses in Japanese boys (aged 9–15 years old) and young Japanese men (aged 16–26 years old) enrolled in NCT01862874 were compared using an analysis of variance model with a response of log-transformed individual titers and a fixed-effect for age group. The statistical criterion required that the lower bound of the two-sided 95% CI of GMT ratio (Japanese boys aged 9–15 years old divided by young Japanese men aged 16–26 years old) be > 0.5 for all four HPV types. Non-inferiority was addressed by two-sided 95% CIs, corresponding to one-sided tests (one corresponding to each HPV type) conducted at the α = 0.025 level (one-sided).

All participants who received at least one vaccination dose and had follow-up data collected were included in the safety analysis. The AEs were summarized as frequencies and percentages of patients following all vaccination visits.

This study enrolled 101 participants to receive the qHPV vaccine and allowed estimation of seroconversion percentage with a 95% CI and a half-width of approximately five percentage points to assess the primary endpoint (based on the assumption of approximately 5% of dropout and/or protocol violation rate). The sample size of 95 boys from this study and 400 young men from the clinical trial in young Japanese adult men (NCT01862874) had > 99% probability that the lower bounds of 95% CI exceeded 0.5 for all HPV types given the underlying true GMT ratio (boys/men) was 1.0, based on the following assumptions for young men from NCT01862874 of no general protocol violation of 95%. Exclusion rate due to Day 1 seropositive or PCR positive between Day 1 and Month 7 to HP6/11/16/18 was approximately 15% and 90% of the randomized participants who completed the vaccination phase.

The statistical analyses were conducted by employees of the study sponsor.

**RESULTS**

**Participants:** Among the 101 enrolled participants, 100 participants completed all three vaccinations and study visits from Day 1 to Month 7. One participant discontinued the study (participant’s decision) and did not receive any vaccination. Demographics and baseline characteristics are presented in Table 1.

Some participants were excluded from their respective PPI populations. Two participants for HPV6/11 were seropositive at Day 1 and missing Month 7 serology sample; one participant for HPV16 missed the Month 7 serology sample; and two participants for HPV18 were seropositive at Day 1 and missed the Month 7 serology sample.

**Immunogenicity:** Among the PPI population, at
Month 7, anti-HPV6/11/16/18 seroconversion rates (95% CIs) were high for each HPV type. The percentage of participants seroconverting to each type was 94.9% (85.5%, 98.3%) for HPV6, 99.0% (94.4%, 100.0%) for HPV11, 99.0% (94.5%, 100.0%) for HPV16, and 99.0% (94.4%, 100.0%) for HPV18 (Table 2).

Anti-HPV6/11/16/18 GMTs at Month 7, were 482.9 mMU/mL, 1052.8 mMU/mL, 3878.3 mMU/mL, and 1114.5 mMU/mL, respectively (Table 2).

The GMT ratios (95% CIs), at Month 7, for Japanese boys (aged 9–15 years old; from this study) versus Japanese men (aged 16–26 years old; NCT01862874) were 1.25 (1.00, 1.57), 2.30 (1.89, 2.78), 1.69 (1.35, 2.11), and 3.05 (2.33, 3.99), for HPV6, HPV11, HPV16, and HPV18, respectively (Table 3). The lower bound of the 95% CI for the GMT ratios was > 0.5 for all four HPV types. These results demonstrated the non-inferiority of the serum antibody response generated by qHPV vaccine in Japanese boys aged 9–15 years old in this study in comparison to Japanese men aged 16–26 years.

### Table 1. Demographics and baseline characteristics (all enrolled participants)

| Characteristics | Median (range)   | Mean (SD)   |
|-----------------|-----------------|-------------|
| BMI (kg/m²)     | 17.7 (12.1–33.1)| 18.2 (3.2)  |
| Weight (kg)     | 53 (21.0–111.4) | 12.2 (2.0)  |
| Age (yr)        | 12.0 (9–16)     | 17.7 (12.1) |
| Male, n (%)     | 53 (52.5)       | 101 (100%)  |
| n (%)           | 101 (100%)      |             |

### Table 2. Summary of anti-HPV cLIA seropositivity rates1) and anti-HPV cLIA GMTs

| Assay (cLIA) | Time point | n1) | m2) | Percent3) (95% CI) | GMT (mMU/mL, 95% CI) |
|--------------|------------|-----|-----|-------------------|----------------------|
| Anti-HPV6    | Day 1      | 98  | 0   | 0.0% (0.0%, 3.7%) | 482.9 (351.1, 664.1) |
|              | Month 7    | 98  | 93  | 94.9% (88.5%, 98.3%) | 1052.8 (851.3, 1302.0) |
| Anti-HPV11   | Day 1      | 98  | 0   | 0.0% (0.0%, 3.7%) | 1052.8 (851.3, 1302.0) |
|              | Month 7    | 98  | 97  | 99.0% (94.4%, 100%) | 3878.3 (2908.5, 5171.6) |
| Anti-HPV16   | Day 1      | 99  | 98  | 99.0% (94.5%, 100%) | 1114.5 (871.6, 1425.1) |
|              | Month 7    | 98  | 97  | 99.0% (94.4%, 100%) | 1114.5 (871.6, 1425.1) |

1) All participants met the inclusion criteria and then were enrolled under the age of 16 yr. The age of participant was tabulated based on the birth month. On the other hand, the enrollment date of five participants was the same month as their 16-yr birthday. Therefore, the age of these participants was aggregated as the age of 16-yr notation.

2) Number of participants randomized to the respective vaccination group who received at least one injection.

3) Number of participants contributing to the analysis.

4) Number of participants seropositive to the relevant HPV type.

5) Percentages are calculated as 100 * (m/n).

6) The CIs for the seropositivity rates are computed based on exact binominal methods proposed by Clopper and Pearson.

7) GMT, geometric mean titer; HPV, human papillomavirus; mMU, milli-Merck units.

| Assay (cLIA) | Time point | n1) | m2) | Percent3) | GMT (mMU/mL) |
|--------------|------------|-----|-----|------------|---------------|
| Anti-HPV6    | Day 1      | 98  | 0   | 0.0% (0.0%, 3.7%) | 482.9 (351.1, 664.1) |
|              | Month 7    | 98  | 93  | 94.9% (88.5%, 98.3%) | 1052.8 (851.3, 1302.0) |
| Anti-HPV11   | Day 1      | 98  | 0   | 0.0% (0.0%, 3.7%) | 1052.8 (851.3, 1302.0) |
|              | Month 7    | 98  | 97  | 99.0% (94.4%, 100%) | 3878.3 (2908.5, 5171.6) |
| Anti-HPV16   | Day 1      | 99  | 98  | 99.0% (94.5%, 100%) | 1114.5 (871.6, 1425.1) |
|              | Month 7    | 98  | 97  | 99.0% (94.4%, 100%) | 1114.5 (871.6, 1425.1) |

### Table 3. Statistical analysis of similarity of anti-HPV cLIA GMTs at Month 7 between Japanese boys aged 9–15 yr and young Japanese men aged 16–26 yr

| Assay (cLIA) | Japanese boys aged 9–15 yr (Group A) (N = 100) | Japanese men aged 16–26 yr (Group B) (N = 561) | Estimated fold difference (Group A / Group B) (95% CI) | p-value for non-inferiority3) |
|--------------|-------------------------------------------------|--------------------------------------------------|------------------------------------------------------|-----------------------------|
| Anti-HPV6    | 98 (351.1, 664.1)                               | 472 (355.7, 416.7)                               | 1.25 (1.00, 1.57)                                    | < 0.001                     |
| Anti-HPV11   | 98 (851.3, 1302.0)                              | 472 (424.8, 494.7)                               | 2.30 (1.89, 2.78)                                    | < 0.001                     |
| Anti-HPV16   | 99 (2908.5, 5171.6)                             | 465 (2110.0, 2495.7)                             | 1.69 (1.35, 2.11)                                    | < 0.001                     |
| Anti-HPV18   | 98 (871.6, 1425.1)                              | 487 (327.1, 408.1)                               | 3.05 (2.33, 3.99)                                    | < 0.001                     |

1) Number of allocated participants who received at least one injection.

2) Number of participants contributing to the analysis.

3) Analyses were based on log-transformed data using an analysis of variance model with a term for age-group. p-value for comparison of the fold difference (Group A / Group B) with the lower bound of 0.5.

CI, confidence interval; cLIA, competitive Luminex immunoassay; GMT, geometric mean titer; HPV, human papillomavirus; mMU, milli-Merck units.
Safety: In Period 1, 70% (n = 70) of participants reported AEs between Days 1–15 following any vaccination (Table 4). Injection-site AEs were reported by 64% (n = 64) of the participants, all of which were considered vaccine-related. The most common injection-site AEs were pain (57%; n = 57), swelling (34%; n = 34), and erythema (31%; n = 31). Systemic AEs were reported by 27% (n = 27) of the participants. The most common systemic AEs were viral upper respiratory tract infection (9%, n = 9) and pyrexia (6%, n = 6). Vaccine-related systemic AEs were reported in 3% (n = 3); all were pyrexia of mild intensity and resolved within two days after onset.

The majority of the injection-site erythema and swelling AEs were 0–2 inches in size, and the majority of the other AEs were mild in intensity. One severe injection-site AE was reported (pain), which resolved on the third day after onset (Table 5).

There were no reported deaths, SAEs, or AEs leading to discontinuation during Part I (Day 1–Month 7) of the study. There were no AEs that were not resolved, and most were resolved within two weeks.

### DISCUSSION

Results of this study suggest that the qHPV vaccine is highly immunogenic in 9–15-years old Japanese boys, with seroconversion to the four HPV types observed among > 95% of the participants. Only one participant did not seroconvert for any of the 4 HPV types. The serum antibody responses elicited by the qHPV vaccine in Japanese boys were non-inferior in comparison to young men from a separate study, thereby supporting the bridging of efficacy findings from Japanese young men (aged 16–26 years old) to Japanese boys (aged 9–15 years old).
Previous studies of young boys (between the ages 9 and 15) have reported similar high immunogenicity with the qHPV vaccine (19,20). In previous post-hoc analyses, immunogenicity in younger males has been shown to be non-inferior to immunogenicity in older males (21). Consistent with this, GMTs were generally higher among the Japanese boys included in this study compared with the young men from a separate study, with GMT ratios ranging from 1.25–3.05 across the HPV types. Antibody responses are known to decline with age, resulting in a shorter duration of protective immunity and reduced antibody affinity in older individuals (22). Given the higher immune responses observed in girls and boys compared with adults receiving 3 doses, the World Health Organization (WHO) recommends a two-dose regimen of HPV vaccine for individuals aged 9–14 years old (23). The similar qHPV vaccine immunogenicity results observed among Japanese boys in this study suggests that a two-dose regimen might be appropriate for Japanese boys.

The qHPV vaccine was generally well-tolerated in this study, with no SAEs, deaths, or AEs leading to discontinuation. The most common AEs were injection-site related and were mostly mild in intensity. The safety profile was generally consistent with previous international clinical trials in boys and girls (19,20) and with the established safety profile of the qHPV vaccine based on the overall clinical trial experience and real-world data since vaccine introduction (23–25).

In 2013, there was an active recommendation from the Ministry of Health, Labour and Welfare to include the HPV vaccine in the National Immunization Program in Japan; however, the recommendation was suspended due to suspected AEs after vaccination (26). No causal association between HPV vaccines and these suspected AEs has been found (27), and the WHO Global Advisory Committee on Vaccine Safety concluded that the available evidence does not indicate any safety concerns for the qHPV vaccine (28).

The HPV vaccine is included in the immunization programs of > 70 countries, at least 11 of which include boys as well as girls (23,29). Implementing qHPV vaccination in males may be beneficial from a health outcome and a cost perspective. The HPV vaccination rates are low, with a cumulative incidence and survival surveillance, epidemiology, and end results experience, 1973-2000. Cancer. 2004;101:281-8.

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Conflict of interest SM, RY, AW, MS and Y Tanaka are all current 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 hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA.
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