Amsterdam, 26 March 2026
EMADOC-1700519818-2799945
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Gardasil 9

Common name: Human papillomavirus 9-valent Vaccine (Recombinant, adsorbed)

Procedure no.: EMA/PAM/0000322285

**Note**

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 26 January 2026 | 2 January 2026 |
| ☐ | CHMP Rapporteur AR | 2 March 2026 | 2 March 2026 |
| ☐ | CHMP comments | 16 March 2026 | 16 March 2026 |
| ☐ | Updated CHMP Rapporteur AR | 19 March 2026 | n/a |
| ☒ | CHMP outcome | 26 March 2026 | 26 March 2026 |

| Abbreviation | Definition |
|---|---|
| 9vHPV | 9-valent human papillomavirus |
| AE | adverse event |
| APaT | all participants as treated |
| CI | confidence interval |
| cLIA | competitive Luminex immunoassay |
| CSR | clinical study report |
| EU | European Union |
| GMT | geometric mean titer |
| HPV | human papilloma virus |
| L1 | major capsid protein |
| MSD | Merck Sharp & Dohme LLC, Rahway, NJ, USA |
| PCR | polymerase chain reaction |
| PPE | per-protocol efficacy |
| PPI | per-protocol immunogenicity |
| qHPV | quadrivalent human papillomavirus |
| RMP | risk management plan |
| SAE | serious adverse event |
| VLP | virus-like particle |

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# 1. Introduction

On 5 January 2026, the MAH submitted a completed paediatric study for Gardasil 9, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that V503-064, a Phase 3, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age is a stand alone study.

## *2.2. Information on the pharmaceutical formulation used in the study*

The commercially available formulation of Gardasil 9 was used in the study. The 9vHPV (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) recombinant vaccine (GARDASIL®9), hereafter referred to as the 9vHPV vaccine, is an aluminum-adjuvanted recombinant Virus Like Particle (VLP) vaccine for the prevention of cancer, dysplasia, genital warts, and persistent infection caused by Human Papilloma Virus (HPV) types that are targeted by the vaccine in individuals from the age of 9 years.

The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. Each 0.5-mL dose is formulated to contain 30/40/60/40/20/20/20/20/20 µg of HPV 6/11/16/18/31/33/45/ 52/58 L1 proteins, respectively. The final product is a sterile suspension for injection in a single-dose vial or a prefilled syringe. For each image, the fill volume permits administration of 0.5 mL of vaccine for intramuscular injection.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- V503-064, a Phase 3, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.

### 2.3.2. Clinical study

**V503-064, a Phase 3, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.**

### Description

V503-064 was a Phase 3, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine in Japanese males, 16 to 26 years of age.

Participants received a 3-dose regimen of either the 9vHPV vaccine or placebo (saline solution) on Day 1, Month 2, and Month 6. This study was conducted at 22 sites in Japan.

The study included 2 stages:

- The Base Study was a case-driven study in which the primary efficacy analysis was conducted after at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases were collected. Immunogenicity and safety were also evaluated.
- The Extension Study occurred after completion of the Base Study; during the Extension Study, participants from the placebo group were offered a 3-dose regimen of the 9vHPV vaccine, and those who did not complete the 3-dose regimen of the 9vHPV vaccine during the Base Study were offered the opportunity to complete a 3-dose series of the 9vHPV vaccine. Safety was evaluated by collecting SAEs.

Three reports summarizing study analyses were submitted:

- Primary analysis CSR: primary efficacy analysis cutoff date was 29-DEC-2023; immunogenicity assessed at Month 7; safety analysis cutoff date was 31-DEC-2023.
- End-of-base-study efficacy analysis report: efficacy analysis only; cutoff date was 16-JUL-2024.
- End-of-study CSR: immunogenicity assessed at Month 36 and safety evaluated in both the Base Study and the Extension Study.

## Methods

### *Study participants*

Eligible participants were healthy Japanese males between the ages of 16 and 26 years who had not previously received an HPV vaccine and who have had up to 5 lifetime sexual partners.

The eligibility criteria for Extension Study included participants who were in the placebo group or those in the V503 group who did not complete the vaccination series in Base Study.

***Treatments***

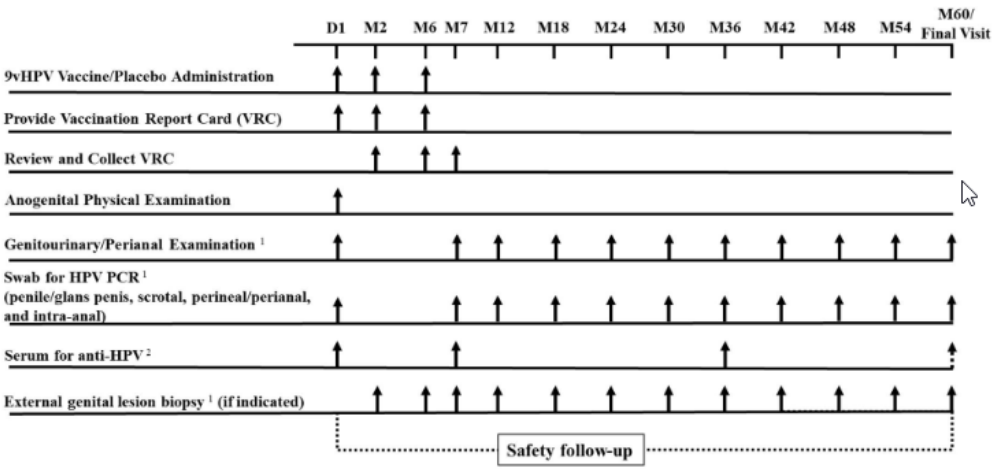
*Table 1. Interventions in study arms*

| Arm Name | Intervention Name | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Vaccination Regimen | Use |
|---|---|---|---|---|---|---|
| V503 | V503 (9vHPV vaccine) | HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose | 0.5 mL | IM | Day 1, Month 2, Month 6 | Test Product |
| Placebo | Saline for injection | 0.9% sodium chloride | 0.5 mL | IM | Day 1, Month 2, Month 6 | Placebo |
| V503 (Ext) | V503 (9vHPV vaccine) | HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose | 0.5 mL | IM | 1 dose in Ext: Day 1 in Ext OR 2 doses in Ext: Day 1 in Ext and Month 4 in Ext | Test Product |
| Placebo (Ext) | V503 (9vHPV vaccine) | HPV 6/11/16/18/31/33/45/52/58 L1 VLP: 30/40/60/40/20/20/20/20/20 mcg per dose | 0.5 mL | IM | Day 1 in Ext, Month 2 in Ext, Month 6 in Ext | Test Product |

9vHPV = 9-valent human papillomavirus (V503); Ext = Extension Study; IM = Intramuscular; VLP = virus-like particle.

*Figure 1. Scheduled treatments and activities during the base study*

Figure 9-1
Study Design (Base Study)



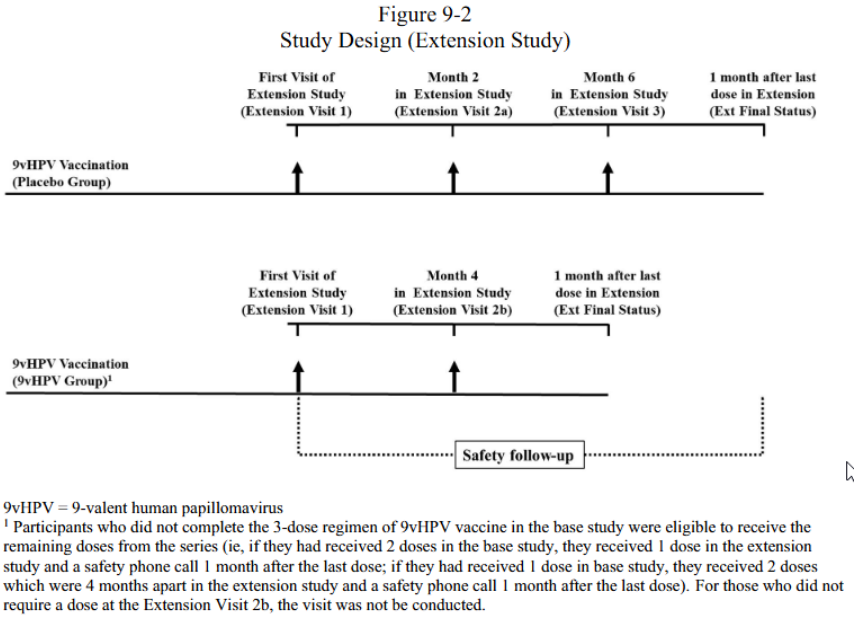

9vHPV = 9-valent human papillomavirus; D = Day; HPV = human papillomavirus; M = Month; PCR = polymerase chain reaction

After at least 17 primary efficacy endpoint cases and at least 17 secondary efficacy endpoint cases were accrued, initial database lock and unblinding was performed and notified to the study sites. Following notification, participants remaining in the study (ie, who have not yet completed a Final Visit) proceeded to the Final Visit in the base study promptly. Under that scenario, participants who had not yet completed a Final Visit completed the specified procedures in Final Visit in this Schedule of Activities.

[1] After initial database lock and unblinding, examination and sample collection for efficacy assessment were not conducted.

[2] Even after initial database lock and unblinding, serum sample was collected. At the Final Visit, serum sample were collected within the specific day ranges from Day 913 to Day 1277 only from the participant who had not yet completed Month 36.

*Figure 2 Scheduled treatments and activities during the extension part of the study*




9vHPV = 9-valent human papillomavirus
[1] Participants who did not complete the 3-dose regimen of 9vHPV vaccine in the base study were eligible to receive the remaining doses from the series (ie, if they had received 2 doses in the base study, they received 1 dose in the extension study and a safety phone call 1 month after the last dose; if they had received 1 dose in base study, they received 2 doses which were 4 months apart in the extension study and a safety phone call 1 month after the last dose). For those who did not require a dose at the Extension Visit 2b, the visit was not be conducted.

***Objectives***

- Primary efficacy objective: to demonstrate that a 3-dose regimen of the 9vHPV vaccine reduced the combined incidence of HPV 6/11/16/18-related anogenital (external genital and intra-anal) persistent infection (≥6 months) compared with placebo in participants who were seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.

- Secondary objectives: 1) to demonstrate that a 3-dose regimen of the 9vHPV vaccine reduced the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection (≥6 months); and 2) to summarize antibody responses to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7 in participants who were seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.

- Primary safety objective: to demonstrate that a 3-dose regimen of the 9vHPV vaccine was generally safe and well tolerated in 16 to 26 year-old Japanese males.

***Outcomes/endpoints***

| Primary Objective | Primary Endpoint |
|---|---|
| **Objective:** To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 6/11/16/18-related anogenital (external genital and intra-anal) persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.<br><br>**Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 6/11/16/18-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%). | HPV 6/11/16/18-related anogenital persistent infection |
| **Objective:** To evaluate the safety and tolerability of the 9vHPV vaccine. | -Solicited injection-site adverse events (AEs)[a]<br><br>-Systemic AEs<br><br>-Serious adverse events (SAEs) |

| Secondary Objectives | Secondary Endpoints |
|---|---|
| **Objective:** To demonstrate that a 3-dose regimen of the 9vHPV vaccine will reduce the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type.<br><br>**Hypothesis:** Administration of a 3-dose regimen of the 9vHPV vaccine reduces the combined incidence of HPV 31/33/45/52/58-related anogenital persistent infection detected in samples from two or more consecutive visits 6 months (± 1-month window) or longer apart compared with placebo (The statistical criterion for success requires that the lower bound of the 2-sided 95% CI of vaccine efficacy is >0%). | HPV 31/33/45/52/58-related anogenital persistent infection |
| **Objective**: To summarize antibody responses [Geometric Mean Titer (GMT) and percent seroconversion] to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Month 7 in participants who are seronegative at Day 1 and PCR-negative Day 1 through Month 7 to the relevant HPV type, by all participants, HM group and MSM group, respectively. | Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 |

[a] Solicited injection-site AEs: redness/erythema, swelling, and tenderness/pain

***Sample size***

The planned enrollment total for this study was 1,050 participants. The targeted enrolment for MSM was approximately 10% of all participants.

Testing the primary efficacy hypothesis with 17 total cases has 94% power to demonstrate that the efficacy of the 9vHPV vaccine compared to placebo is greater than 0% at 1-sided type 1 error rate ≤ 0.025 if the underlying true VE against the primary efficacy endpoint is at least 85%.

Testing the secondary efficacy hypothesis with 17 total cases has also 94% power to demonstrate that the efficacy of the 9vHPV vaccine compared to placebo is greater than 0% at an overall 1-sided type 1 error rate ≤ 0.025 if the underlying true VE against the secondary endpoint is at least 85%. A total of approximately 1050 participants are needed to be enrolled in order to accumulate approximately 17 total primary endpoint cases and at least 17 total secondary efficacy endpoint cases within 56 months from the time the first study participant signs the ICF.

***Randomisation and blinding (masking)***

Intervention randomization will be stratified according to the following factors:

1. Heterosexual Men (HM) or Men who have sex with Men (MSM).

Even though randomization will be stratified by HM and MSM, the test of the primary and secondary efficacy hypotheses will not be stratified by HM and MSM. Stratification is intended to support immunogenicity analysis within HM and MSM, to avoid unbalanced allocation between the vaccination groups particularly in the MSM cohort.

A double-blinding technique will be used to ensure blinding of the study. The 9vHPV vaccine (V503) and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the clinical evaluation of the participants are unaware of the intervention assignments.

For the primary and secondary efficacy analyses, the database may be unblinded prior to the end of study, and the Sponsor personnel will be unblinded to participant vaccination group assignments. However, laboratory personnel, the pathology panel, the investigators, site personnel and participants will remain blinded to whether participants received the 9vHPV vaccine or placebo throughout the entire study period.

***Statistical Methods***

Statistical Methods for Efficacy Analyses: The primary efficacy hypothesis was evaluated by comparing the 9vHPV vaccine with placebo with respect to the primary efficacy endpoint. The p-value for testing the hypothesis that vaccine efficacy was greater than 0% as well as 95% CI for vaccine efficacy were provided using the exact binomial method proposed by Chan and Bohidar (1998)[1]. The statistical criterion for success required that the lower bound of the 2-sided 95% CI for vaccine efficacy against the primary efficacy endpoint was greater than 0%. The secondary efficacy hypothesis was evaluated by comparing the 9vHPV vaccine with placebo with respect to the secondary efficacy endpoint based on the same method as that used in testing the primary efficacy hypothesis. The statistical criterion for success required that the lower bound of the 2-sided 95% CI for vaccine efficacy against the secondary efficacy was greater than 0%.

Multiplicity: The overall type 1 error rate associated with testing the primary and secondary efficacy hypotheses will be controlled to not exceed 0.025 (1-sided) by a fixed sequence procedure. The

[1] Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. Commun Statist Theory Meth 1998;27(6):1305-22.

secondary efficacy hypothesis will be tested only if the primary efficacy hypothesis is successfully demonstrated.

Statistical Methods for Immunogenicity: The secondary immunogenicity objective will be addressed by summarizing antibody titer responses measured using cLIA at Month 7. The GMTs and the corresponding 95% CIs will be estimated based on the t-distribution for HPV types of 6, 11, 16, 18, 31, 33, 45, 52, and 58. Point estimates and the corresponding 95% CIs of percent seroconversion will be provided using the exact binomial method of Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934] for HPV types of 6, 11, 16, 18, 31, 33, 45, 52, and 58, for all participants, HM group and MSM group, respectively.

## Results

### *Participant flow*

Base Study: A total of 1059 participants were enrolled (529 in the 9vHPV vaccine group; 530 in the placebo group), and all received at least 1 dose of 9vHPV vaccine. Most participants completed the 3-dose regimen (514 participants in the 9vHPV vaccine group; 508 in the placebo group). Overall, 936 participants (88.4%) completed the study (87.7% [n=464] in the 9vHPV vaccine group; 89.1% [n=472] in the placebo group). The most common reason for discontinuation was withdrawal by subject.

*Table 2. Disposition of Participants, base study.*

Table 10-1
Disposition of Participants
(Day 1 to End of Base Study)
(All Enrolled Participants) (P064 Base Study)

| | V503 | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Not Randomized | | | | | 12 | |
| Participants in population | 529 | | 530 | | 1,059 | |
| **Vaccinated at** | | | | | | |
| Treatment 1 | 529 | (100.0) | 530 | (100.0) | 1,059 | (100.0) |
| Treatment 2 | 523 | (98.9) | 518 | (97.7) | 1,041 | (98.3) |
| Treatment 3 | 514 | (97.2) | 508 | (95.8) | 1,022 | (96.5) |
| **Trial Disposition** | | | | | | |
| Completed | 464 | (87.7) | 472 | (89.1) | 936 | (88.4) |
| Discontinued | 65 | (12.3) | 58 | (10.9) | 123 | (11.6) |
| Lost To Follow-Up | 8 | (1.5) | 16 | (3.0) | 24 | (2.3) |
| Withdrawal By Subject | 57 | (10.8) | 42 | (7.9) | 99 | (9.3) |
| **Trial Completer** | | | | | | |
| Started | 464 | | 472 | | 936 | |
| Continuing Into Extension Study | 2 | (0.4) | 381 | (80.7) | 383 | (40.9) |
| Not Continuing Into Extension Study | 462 | (99.6) | 91 | (19.3) | 553 | (59.1) |
| **Participant Study Medication Disposition** | | | | | | |
| Completed | 514 | (97.2) | 508 | (95.8) | 1,022 | (96.5) |
| Discontinued | 15 | (2.8) | 22 | (4.2) | 37 | (3.5) |
| Lost To Follow-Up | 0 | (0.0) | 4 | (0.8) | 4 | (0.4) |
| Physician Decision | 0 | (0.0) | 1 | (0.2) | 1 | (0.1) |
| Withdrawal By Subject | 15 | (2.8) | 17 | (3.2) | 32 | (3.0) |
| Started=Base-study completion; | | | | | | |

Source: [P064V503: adam-adsl; adex]

Extension Study: 383 participants entered the extension (2 in the 9vHPV vaccine group; 381 in the placebo group) and received at least 1 dose of 9vHPV vaccine. Both participants in the 9vHPV vaccine

group completed the 3-dose regimen and the study; in the placebo group, 367 participants completed the 3-dose regimen and the study. Overall, 369 participants completed the Extension Study (2 in the 9vHPV vaccine group; 367 in the placebo group). The most common reason for discontinuation was withdrawal by subject.

*Table 3. Disposition of Participants, extension study*

Table 10-2
Disposition of Participants
(Extension Day 1 to End of Extension Study)
(All Enrolled Participants) (P064 Extension Study)

| | V503 | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 2 | | 381 | | 383 | |
| **Vaccinated at** | | | | | | |
| Extension 1 | 2 | (100.0) | 381 | (100.0) | 383 | (100.0) |
| Extension 2 | 1 | (50.0) | 373 | (97.9) | 374 | (97.7) |
| Extension 3 | 0 | (0.0) | 367 | (96.3) | 367 | (95.8) |
| **Trial Disposition** | | | | | | |
| Completed | 2 | (100.0) | 367 | (96.3) | 369 | (96.3) |
| Discontinued | 0 | (0.0) | 14 | (3.7) | 14 | (3.7) |
| Lost To Follow-Up | 0 | (0.0) | 3 | (0.8) | 3 | (0.8) |
| Physician Decision | 0 | (0.0) | 1 | (0.3) | 1 | (0.3) |
| Withdrawal By Subject | 0 | (0.0) | 10 | (2.6) | 10 | (2.6) |
| **Participant Study Medication Disposition** | | | | | | |
| Completed | 2 | (100.0) | 367 | (96.3) | 369 | (96.3) |
| Discontinued | 0 | (0.0) | 14 | (3.7) | 14 | (3.7) |
| Lost To Follow-Up | 0 | (0.0) | 3 | (0.8) | 3 | (0.8) |
| Physician Decision | 0 | (0.0) | 1 | (0.3) | 1 | (0.3) |
| Withdrawal By Subject | 0 | (0.0) | 10 | (2.6) | 10 | (2.6) |
| Arms for which the participants were randomized in Base Study. | | | | | | |

Source: [P064V503: adam-adsl; adex]

***Recruitment***

| | |
|---|---|
| First Participant First Visit | 30-NOV-2020 first participant first visit |
| Study Completion Date | 23-JUL-2025 last participant last visit |

***Baseline data***

- Overall Mean Age (Standard Deviation): 22.9 years (2.1 years)
- Sex: 1,059 (100%) male
- Sexual Orientation: 947 (89.4%) HM, 112 (10.6%) MSM
- Race: 1,059 (100%) Japanese

*Table 4. Participants demographic characteristics.*

Table 10-5
Participant Characteristics
(All Randomized Participants Population) (P064)

| | V503 | | Placebo | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Participants in population | 529 | | 530 | | 1,059 | |
| **Sex** | | | | | | |
| Male | 529 | (100.0) | 530 | (100.0) | 1,059 | (100.0) |
| **Age (Years)** | | | | | | |
| 16 to 20 | 87 | (16.4) | 83 | (15.7) | 170 | (16.1) |
| 21 to 26 | 442 | (83.6) | 447 | (84.3) | 889 | (83.9) |
| Mean | 22.9 | | 22.8 | | 22.9 | |
| SD | 2.1 | | 2.1 | | 2.1 | |
| Median | 23.0 | | 23.0 | | 23.0 | |
| Range | 16 to 27 | | 16 to 27 | | 16 to 27 | |
| **Race** | | | | | | |
| Asian | 529 | (100.0) | 530 | (100.0) | 1,059 | (100.0) |
| **Ethnicity** | | | | | | |
| Not Hispanic Or Latino | 529 | (100.0) | 530 | (100.0) | 1,059 | (100.0) |
| **Smoking Status** | | | | | | |
| Current Smoker | 119 | (22.5) | 143 | (27.0) | 262 | (24.7) |
| Ex Smoker | 36 | (6.8) | 58 | (10.9) | 94 | (8.9) |
| Never Smoked | 374 | (70.7) | 329 | (62.1) | 703 | (66.4) |
| **Sexual Orientation** | | | | | | |
| HM | 473 | (89.4) | 474 | (89.4) | 947 | (89.4) |
| MSM | 56 | (10.6) | 56 | (10.6) | 112 | (10.6) |
| **Lifetime Sexual Partners** | | | | | | |
| 0 | 2 | (0.4) | 1 | (0.2) | 3 | (0.3) |
| 1 to 4 | 381 | (72.0) | 390 | (73.6) | 771 | (72.8) |
| >4 | 146 | (27.6) | 139 | (26.2) | 285 | (26.9) |

SD=Standard deviation.
Participants were confirmed to be between 16-26 years of age; calculated age may be out of range (16-26) due to masking of date of birth.
HM=Heterosexual males; MSM=Males who have sex with males;

Source: [P064V01V503: adam-adsl]

***Number analysed***

Only HPV negative subjects for certain HPV types at the baseline were included to the analysis.

*Table 5 Efficacy Analysis population at base study*

| | V503 (N=529) | Placebo (N=530) | Total (N=1,059) |
|---|---|---|---|
| **Number of Participants who received at least 1 vaccination[a]** | **529** | **530** | **1,059** |
| **Eligible for the PPE Analysis Related to** | | | |
| HPV 6/11 | 419 | 377 | 796 |
| HPV 16 | 473 | 463 | 936 |
| HPV 18 | 438 | 423 | 861 |
| HPV 31 | 459 | 445 | 904 |
| HPV 33 | 475 | 458 | 933 |
| HPV 45 | 462 | 449 | 911 |
| HPV 52 | 461 | 448 | 909 |
| HPV 58 | 480 | 475 | 955 |

*Table 6 Immunogenicity Analysis Population at Base study*

| | V503 (N=529) | Placebo (N=530) | Total (N=1,059) |
|---|---|---|---|
| **Number of Participants who received at least 1 vaccination[a]** | **529** | **530** | **1,059** |
| **Eligible for the PPI Analysis Related to** | | | |
| HPV 6/11 | 399 | 367 | 766 |
| HPV 16 | 449 | 446 | 895 |
| HPV 18 | 417 | 411 | 828 |
| HPV 31 | 435 | 429 | 864 |
| HPV 33 | 451 | 442 | 893 |
| HPV 45 | 439 | 434 | 873 |
| HPV 52 | 437 | 433 | 870 |
| HPV 58 | 456 | 458 | 914 |

***Efficacy results***

In the PPE population, the efficacy of the 9vHPV vaccine against HPV 6/11/16/18-related anogenital persistent infection was 89.3% (95% CI: 55.4, 98.2) in the primary analysis and 91.6% (95% CI: 67.7, 98.6) in the end-of-base-study analysis.

In the PPE population, the efficacy of the 9vHPV vaccine against HPV 31/33/45/52/58-related anogenital persistent infection was 63.5% (95% CI: 2.7, 86.0) in the primary analysis and 72.9% (95% CI: 38.7, 89.3) in the end-of-base-study analysis.

*Table 7. Summary of Efficacy to prevent persistent HPV infection in young Japanese males.*

Table 1-1
Summary of Efficacy of 9vHPV Vaccine in Japanese Men 16 to 26 Years of Age
(Per-Protocol Efficacy Population)

| Endpoint | VE (95% CI) | |
|---|---|---|
| | At Testing of the Primary and Secondary Efficacy Hypotheses[a] | At End of Efficacy Follow-up During the Study[b] |
| **Primary** | | |
| HPV 6/11/16/18-related anogenital persistent infection (≥ 6 months) | 89.3% (95% CI: 55.4, 98.2) | 91.6% (95% CI: 67.7, 98.6) |
| **Secondary** | | |
| HPV 31/33/45/52/58-related anogenital persistent infection (≥ 6 months) | 63.5% (95% CI: 2.7, 86.0) | 72.9% (95% CI: 38.7, 89.3) |
| **Exploratory** | | |
| HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection (≥ 6 months) | 74.3% (95% CI: 44.5, 89.3) | 79.0% (95% CI: 57.7, 90.0) |
| HPV 6/11/16/18/31/33/45/52/58-related anogenital persistent infection (≥ 12 months) | 85.5% (95% CI: 54.6, 96.3) | 82.5% (95% CI: 50.3, 94.5) |
| HPV 6/11/16/18/31/33/45/52/58-related genital warts, PIN, penile, perianal or perineal cancer | 83.6% (95% CI: -22.2, 99.3) | 83.6% (95% CI: -22.0, 99.3) |
| HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection (≥ 6 months) | 67.3% (95% CI: -75.4, 95.2) | 80.5% (95% CI: 18.3, 96.9) |
| HPV 6/11/16/18/31/33/45/52/58-related intra-anal persistent infection (≥ 12 months) | 50.9% (95% CI: -527.3, 98.3) | 51.0% (95% CI: -526.3, 98.3) |
| HPV 6/11/16/18/31/33/45/52/58-related external genital persistent infection (≥ 6 months) | 79.4% (95% CI: 51.6, 91.6) | 83.3% (95% CI: 62.4, 93.1) |
| HPV 6/11/16/18/31/33/45/52/58-related external genital persistent infection (≥12 months) | 89.8% (95% CI: 58.5, 98.3) | 86.3% (95% CI: 57.1, 96.5) |

[a] Efficacy data through December 29, 2023.
[b] Efficacy data through July 16, 2024.

Immunogenicity results

*Anti-HPV cLIA Geometric Mean Titers*

Antibody responses to HPV 6, 11,16, 18, 31, 33, 45, 52, and 58 were measured using the cLIA at Day 1, Month 7, and Month 36. In the PPI population, anti-HPV GMTs for each HPV type were induced at Month 7 and decreased from Month 7 to Month 36.

*Table 8. Antibody titer change from baseline (D1), 1-month post third dose (M7) up to 36 months from the study start.*

Table 11-1
Summary of Geometric Mean Titers
(Per-Protocol Immunogenicity Population) (P064 Base Study)

| Assay (cLIA) | Time Point | V503 (N=529) n | V503 GMT (mMU/mL) | V503 (95% CI) | Placebo (N=530) n | Placebo GMT (mMU/mL) | Placebo (95% CI) |
|---|---|---|---|---|---|---|---|
| Anti-HPV 6 | Day 1 | 399 | 24.0 | (22.8, 25.3) | 367 | 24.5 | (23.1, 25.9) |
| | Month 7 | 399 | 927.3 | (850.2, 1011.3) | 367 | 21.1 | (< 20, 22.5) |
| | Month 36 | 371 | 99.4 | (88.5, 111.6) | 342 | < 20 | (< 20, < 20) |
| Anti-HPV 11 | Day 1 | 399 | < 16 | (< 16, < 16) | 367 | < 16 | (< 16, < 16) |
| | Month 7 | 399 | 716.5 | (654.4, 784.5) | 367 | < 16 | (< 16, < 16) |
| | Month 36 | 371 | 71.7 | (64.2, 80.2) | 342 | < 16 | (< 16, < 16) |
| Anti-HPV 16 | Day 1 | 449 | < 20 | (< 20, < 20) | 446 | < 20 | (< 20, < 20) |
| | Month 7 | 449 | 3491.6 | (3196.5, 3814.0) | 446 | < 20 | (< 20, < 20) |
| | Month 36 | 414 | 318.9 | (284.3, 357.7) | 417 | < 20 | (., .) |
| Anti-HPV 18 | Day 1 | 417 | 49.6 | (48.4, 50.9) | 411 | 50.1 | (48.8, 51.5) |
| | Month 7 | 417 | 998.0 | (904.3, 1101.4) | 411 | 45.5 | (43.4, 47.7) |
| | Month 36 | 387 | 67.3 | (59.2, 76.5) | 385 | < 24 | (< 24, < 24) |
| Anti-HPV 31 | Day 1 | 435 | 14.3 | (13.5, 15.1) | 429 | 14.1 | (13.2, 14.9) |
| | Month 7 | 435 | 832.1 | (753.3, 919.2) | 429 | 15.4 | (14.3, 16.5) |
| | Month 36 | 397 | 82.9 | (73.2, 93.8) | 400 | < 10 | (< 10, < 10) |
| Anti-HPV 33 | Day 1 | 451 | 12.7 | (12.2, 13.1) | 442 | 12.5 | (12.0, 13.0) |
| | Month 7 | 451 | 489.8 | (448.6, 534.7) | 442 | 12.7 | (11.9, 13.4) |
| | Month 36 | 413 | 46.4 | (41.4, 52.0) | 414 | < 8 | (< 8, < 8) |
| Anti-HPV 45 | Day 1 | 439 | < 8 | (< 8, 8.2) | 434 | < 8 | (< 8, 8.2) |
| | Month 7 | 439 | 326.6 | (293.7, 363.2) | 434 | 8.5 | (< 8, 9.0) |
| | Month 36 | 404 | 27.4 | (24.1, 31.1) | 406 | < 8 | (< 8, < 8) |
| Anti-HPV 52 | Day 1 | 437 | 10.8 | (10.3, 11.3) | 433 | 11.0 | (10.4, 11.5) |
| | Month 7 | 437 | 390.5 | (356.3, 428.0) | 433 | 10.1 | (9.5, 10.8) |
| | Month 36 | 404 | 45.6 | (40.8, 50.9) | 405 | < 8 | (< 8, < 8) |
| Anti-HPV 58 | Day 1 | 456 | < 8 | (< 8, < 8) | 458 | < 8 | (< 8, < 8) |
| | Month 7 | 456 | 588.3 | (537.7, 643.6) | 458 | < 8 | (< 8, < 8) |
| | Month 36 | 421 | 61.6 | (55.4, 68.5) | 430 | < 8 | (< 8, < 8) |

N=Number of participants who received at least 1 vaccination.
n=Number of participants contributing to the analysis.
CI=Confidence interval; cLIA=Competitive Luminex immunoassay; GMT=Geometric mean titer; mMU=milli-Merck Units;

Source: [P064V503: adam-adsl; adimm]

*Seropositivity rate*

The percent seroconversion for each vaccine-targeted HPV type ranged from 98.9% to 99.8% at Month 7. At Month 36, the percentage of participants who were seropositive ranged from 74.2% to 95.7 % depending on the HPV types in the V503 group.

*Table 9 Seropositivity rate change from baseline (D1), 1-month post third dose (M7) up to 36 months from the study start.*

Table 11-2
Summary of Anti-HPV cLIA Seropositivity Rates
(Per-Protocol Immunogenicity Population) (P064 Base Study)

| | | V503 (N=529) | | | | Placebo (N=530) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Seropositive | | | | Seropositive | |
| Assay (cLIA) | Time Point | n | m | Percent | (95% CI) | n | m | Percent | (95% CI) |
| Anti-HPV 6 | Day 1 | 399 | 0 | 0.0 | (0.0, 0.9) | 367 | 0 | 0.0 | (0.0, 1.0) |
| | Month 7 | 399 | 398 | 99.7 | (98.6, 100.0) | 367 | 13 | 3.5 | (1.9, 6.0) |
| | Month 36 | 371 | 309 | 83.3 | (79.1, 86.9) | 342 | 5 | 1.5 | (0.5, 3.4) |
| Anti-HPV 11 | Day 1 | 399 | 0 | 0.0 | (0.0, 0.9) | 367 | 0 | 0.0 | (0.0, 1.0) |
| | Month 7 | 399 | 398 | 99.7 | (98.6, 100.0) | 367 | 15 | 4.1 | (2.3, 6.7) |
| | Month 36 | 371 | 301 | 81.1 | (76.8, 85.0) | 342 | 3 | 0.9 | (0.2, 2.5) |
| Anti-HPV 16 | Day 1 | 449 | 0 | 0.0 | (0.0, 0.8) | 446 | 0 | 0.0 | (0.0, 0.8) |
| | Month 7 | 449 | 447 | 99.6 | (98.4, 99.9) | 446 | 19 | 4.3 | (2.6, 6.6) |
| | Month 36 | 414 | 396 | 95.7 | (93.2, 97.4) | 417 | 0 | 0.0 | (0.0, 0.9) |
| Anti-HPV 18 | Day 1 | 417 | 0 | 0.0 | (0.0, 0.9) | 411 | 0 | 0.0 | (0.0, 0.9) |
| | Month 7 | 417 | 414 | 99.3 | (97.9, 99.9) | 411 | 34 | 8.3 | (5.8, 11.4) |
| | Month 36 | 387 | 287 | 74.2 | (69.5, 78.5) | 385 | 4 | 1.0 | (0.3, 2.6) |
| Anti-HPV 31 | Day 1 | 435 | 0 | 0.0 | (0.0, 0.8) | 429 | 0 | 0.0 | (0.0, 0.9) |
| | Month 7 | 435 | 430 | 98.9 | (97.3, 99.6) | 429 | 24 | 5.6 | (3.6, 8.2) |
| | Month 36 | 397 | 356 | 89.7 | (86.3, 92.5) | 400 | 4 | 1.0 | (0.3, 2.5) |
| Anti-HPV 33 | Day 1 | 451 | 0 | 0.0 | (0.0, 0.8) | 442 | 0 | 0.0 | (0.0, 0.8) |
| | Month 7 | 451 | 450 | 99.8 | (98.8, 100.0) | 442 | 49 | 11.1 | (8.3, 14.4) |
| | Month 36 | 413 | 372 | 90.1 | (86.8, 92.8) | 414 | 1 | 0.2 | (0.0, 1.3) |
| Anti-HPV 45 | Day 1 | 439 | 0 | 0.0 | (0.0, 0.8) | 434 | 0 | 0.0 | (0.0, 0.8) |
| | Month 7 | 439 | 434 | 98.9 | (97.4, 99.6) | 434 | 39 | 9.0 | (6.5, 12.1) |
| | Month 36 | 404 | 303 | 75.0 | (70.5, 79.1) | 406 | 1 | 0.2 | (0.0, 1.4) |
| Anti-HPV 52 | Day 1 | 437 | 0 | 0.0 | (0.0, 0.8) | 433 | 0 | 0.0 | (0.0, 0.8) |
| | Month 7 | 437 | 432 | 98.9 | (97.4, 99.6) | 433 | 18 | 4.2 | (2.5, 6.5) |
| | Month 36 | 404 | 352 | 87.1 | (83.5, 90.2) | 405 | 2 | 0.5 | (0.1, 1.8) |
| Anti-HPV 58 | Day 1 | 456 | 0 | 0.0 | (0.0, 0.8) | 458 | 0 | 0.0 | (0.0, 0.8) |
| | Month 7 | 456 | 453 | 99.3 | (98.1, 99.9) | 458 | 7 | 1.5 | (0.6, 3.1) |
| | Month 36 | 421 | 397 | 94.3 | (91.6, 96.3) | 430 | 4 | 0.9 | (0.3, 2.4) |

Positive by serology is defined as having an anti-HPV cLIA titer ≥ the serostatus cutoff values of 65, 37, 79, 85, 46, 26, 21, 30 and 31 milli-Merck Units/mL for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58, respectively at Day 1 and Month 7.

Positive by serology is defined as having an anti-HPV cLIA titer ≥ the serostatus cutoff values of 34, 25, 32, 26, 15, 10, 10, 14 and 10 milli-Merck Units/mL for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58, respectively at Month 36.

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

The CIs are computed based on exact binominal methods proposed by Clopper and Pearson.

N=Number of participants randomized to the respective vaccination group who received at least 1 vaccination.

n=Number of participants contributing to the analysis.

m=Number of participants seropositive to the relevant HPV type.

CI=Confidence interval; cLIA=Competitive Luminex immunoassay;

Source: [P064V503: adam-adsl; adimm]

***Safety results***

Safety analysis was conducted in the all participants as treated (APaT )population, which included all 1059 randomized participants (529 in the 9vHPV vaccine group; 530 in the placebo group) who received at least 1 dose of vaccine or placebo and had follow-up data.

In the Base Study, safety events were collected following each vaccination, including elevated temperatures (Days 1 through 5), all injection-site and systemic AEs (Days 1 through 15), SAEs (Day 1 through Month 6 after the last dose of vaccination), and deaths and vaccine-related SAEs (entire study duration).

In the Extension Study SAEs and deaths were collected from the first dose of vaccination until 1 month after the last dose.

Safety Results

During the Base Study, the proportions of participants with AEs were higher in the 9vHPV vaccine group (73.5%) compared with the placebo group (44.3%).

Injection-site Adverse Events

Overall, 69.8% of participants in the 9vHPV vaccine group reported at least 1 injection site AE within 5 days following any vaccination visit, compared with 29.6% in the placebo group. The most common injection-site AEs in the 9vHPV vaccine group were pain (67.5%), swelling (22.1%), and erythema (19.5%); in the placebo group, these were pain (23.0%), erythema (13.2%), and swelling (7.5%).

Most injection-site AEs within 5 days following any vaccination visit were mild in intensity; no injection-site AEs of severe intensity were reported. Most of the injection-site erythema and swelling AEs were ≤2 inches in size in both vaccination groups.

Systemic Adverse Events

Overall, 20.2% of participants in the 9vHPV vaccine group and 19.8% of participants in the placebo group reported at least 1 systemic AE within 15 days following any vaccination visit. The most common systemic AEs (≥2% in any vaccination group) were pyrexia (9vHPV vaccine group: 5.5%, placebo: 6.2%) and headache (4.3% in each vaccination group).

Overall, 11.0% of participants in the 9vHPV vaccine group and 9.8% of participants in the placebo group reported at least 1 vaccine-related systemic AE within 15 days following any vaccination visit. The most common vaccine-related systemic AEs (≥2.0% in any vaccination any group) were pyrexia (9vHPV vaccine group: 4.2%, placebo: 4.3%) and headache (9vHPV vaccine group: 3.0%, placebo: 2.8%).

The severity of systemic AEs and vaccine related systemic AEs within 15 days following any vaccination visit were similar between the 2 vaccination groups. Most systemic AEs in both vaccination groups were mild to moderate in severity.

Serious Adverse Events

SAEs were reported for 12 participants during the Base Study (7 in the 9vHPV vaccine group and 5 in the placebo group) and for 2 participants in the placebo group during the Extension Study after receiving 9vHPV vaccine. All SAEs resolved, and none were considered vaccine-related. No deaths were reported during the entire study.

Discontinuations Due to AEs

No participants discontinued study vaccination due to an AE.

### 2.3.3. Discussion on clinical aspects

The age cohort below 19 years of age, which classifies as paediatric, was limited in this study. Only 170 subjects were in age group 16-20 and the exact number of 16-18 year olds participating the study remains unknown. Therefore, current study has limited impact for evaluating efficacy and safety of Gardasil9 in paediatric population.

Anyhow, the results of V503-064 demonstrated that the 9vHPV vaccine is efficacious in preventing both HPV 6/11/16/18-related and HPV 31/33/45/52/58-related anogenital persistent infection (≥ 6 months) in Japanese men aged 16 to 26 years old. The vaccine efficacy against HPV 6/11/16/18-related persistent infection and external genital lesions in this study was similar to that observed for the qHPV (Gardasil4) vaccine in other studies conducted inside and outside Japan.

Administration of a 3-dose regimen of the 9vHPV vaccine induced antibody responses to all HPV types that generally persisted through 36 months after the first vaccination. The data in this application are consistent with prior findings, demonstrating immunogenicity of the 9vHPV vaccine in Japanese men aged 16 to 26 years old.

Administration of a 3-dose regimen of the 9vHPV vaccine administered to Japanese men aged 16 to 26 years was generally well tolerated. The safety profile in this study did not reveal any new findings compared with previous clinical and post licensure studies of the 9vHPV vaccine. Therefore, there were no safety findings that would indicate any changes to the safety profile of the 9vHPV vaccine.

# 3. CHMP overall conclusion and recommendation

The results of this study indicate no new efficacy or safety concern. The P46 procedure is considered fulfilled.

☒ **Fulfilled:**

No regulatory action required.