Amsterdam, 26 March 2026
EMADOC-1700519818-2792268
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/0000321314

**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 Jan 2026 | 26 Jan 2026 |
| ☐ | CHMP Rapporteur AR | 2 March 2026 | 03 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 papillomavirus |
| IgG LIA | immunoglobulin G Luminex immunoassay |
| L1 | major capsid protein |
| MSD | Merck Sharp & Dohme LLC, Rahway, NJ, USA |
| NMPA | National Medical Products Administration |
| PPI | per-protocol immunogenicity |
| RMP | risk management plan |
| SAE | serious adverse event |
| VLP | virus-like particle |
| VRC | Vaccination Report Card |

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# 1. Introduction

On 18 December 2025, 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 P024X01V503: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 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:

- P024X01V503: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age

### 2.3.2. Clinical study

**P024X01V503: A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity and Safety of 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine (V503) in Chinese females 9 to 45 Years of Age**

### Description

The 9vHPV vaccine was approved in China in April 2018 for the prevention against persistent infections, cervical precancerous or dysplastic lesions and cancer caused by vaccine-targeted HPV types in women 16 to 26 years of age.

Protocol V503-024 was conducted in China to evaluate the immunogenicity and safety of the 9vHPV vaccine in females aged 9 to 45 years who received 3 doses (Day 1, Month 2, and Month 6) to support indication extension to include Chinese females aged 9 to 15 years and 27 to 45 years. V503-024 was a Phase 3, non-randomized, multi-site, open-label study.

## Methods

### *Study participants*

Key criteria for inclusion in Stage I:

- Healthy Chinese females aged 9 and 45 years (inclusive).
- Participant has a lifetime history of 0 to 4 male and/or female sexual partners at the time of enrolment.
- Using effective contraception through 7 months of study period

Key criteria for inclusion in Stage II include:

- Participant was enrolled in Stage I.
- Participant was 9 to 19 years of age at enrollment in Stage I.
- Participant had completed 3 doses of the study vaccination.

### *Treatments*

*Table 1 Study Treatments*

| Study Treatment Name | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Vaccination Regimen | Use | IMP/NIMP | Sourcing |
|---|---|---|---|---|---|---|---|---|
| 9vHPV vaccine, also known as V503 | Liquid in vial | 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 per dose | Intramuscular injection | Day 1, Month 2, and Month 6* | Experimental | IMP | Provided centrally by the Sponsor |
| Definition Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.<br>*: For the first 25 participants enrolled in the 9-15 years old group, the safety from 1st dose through Day 15 following 2nd dose will be evaluated by a DMC. If the safety is favorable, this subset of participant will receive the 3rd dose and enrollment of the rest of participants in the 9-15 years old group will be initiated. | | | | | | | | |

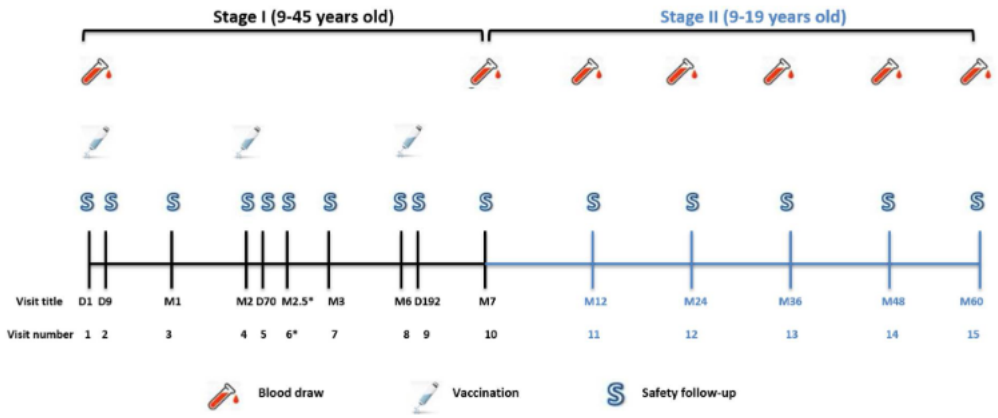
A single batch of the 9vHPV vaccine was used in this study. Serum samples were obtained from each participant at Day 1 and Visit 10 (1 month post Dose 3) in Stage I. Participants enrolled in the 9 to 19 years old group who received 3 doses of study vaccination during Stage I were eligible to participate in Stage II and followed up to Month 60 visit (approximately 54 months post Dose 3). Serum samples were to be obtained at Month 12, Month 24, Month 36, Month 48, and Month 60 visits. All serum samples were to be tested by cLIA and IgG LIA for measurement of anti-HPV antibodies for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 to fulfil the primary objectives. As an exploratory objective, PBNA was to be performed on serum samples collected from the same subset of participants in the 9 to 19 years old group selected for PBNA testing during Stage I. SAEs (regardless of causality), cancers, pregnancy events, infant SAEs, new medical conditions, and CPA were to be collected throughout the entire period of Stage II.

Because of the COVID-19 pandemic, the visit window for Dose 3 was extended to minimize disruptions. The original Dose 3 window (Month 6 ± 28 days) was extended to 155 to 364 days after Dose 1 to allow completion of the 3-dose regimen within 1 year, consistent with the approved label in China. A supportive immunogenicity analysis was performed in Stage I to assess the potential impact of this

change in vaccination schedule. The analysis confirmed that this modification did not impact the primary immunogenicity hypothesis.

*Figure 1. Study design*

Figure 9-1
Study Diagram




*: Visit 6 (Month 2.5) was only applicable to the first 25 participants enrolled in the 9-15 years old group who were evaluated for safety from 1st dose through Day 15 following 2nd dose by the Data Monitoring Committee (DMC). If safety evaluation was found favorable, the 25 girls evaluated for safety would receive the 3rd dose and enrollment of the rest of participants 9 to 15 years of age would be initiated.

***Objectives***

Stage I – Primary:

- To demonstrate that administration of 9vHPV vaccine induced noninferior **GMTs** for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 assessed by cLIA in females **9 to 19** years of age compared with females **20 to 26** years of age. The statistical criterion for non inferiority required that the lower bound of 2-sided 97.5% CI of GMT ratio (females 9 to 19 years of age vs. females 20 to 26 years of age) was >0.67 for each HPV type.

- To demonstrate that administration of the 9vHPV vaccine induced noninferior **seroconversion** percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 assessed by cLIA in females **27 to 45** years of age compared with females **20 to 26** years of age. The statistical criterion for noninferiority required that the lower bound of 2 sided 97.5% CI for the difference (females 27 to 45 years of age minus females 20 to 26 years of age) in seroconversion percentages was >-5% for each HPV type.

Key Secondary:

- To demonstrate that administration of the 9vHPV vaccine induced noninferior **seroconversion** percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 assessed by cLIA in females **9 to 19** years of age compared with females **20 to 26** years of age. The statistical criterion for non inferiority required that the lower bound of 2-sided 97.5% CI for the difference (females 9 to 19 years of age minus females 20 to 26 years of age) in seroconversion percentages was >-5% for each HPV type.

- To demonstrate that administration of the 9vHPV vaccine induced noninferior **GMTs** for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 assessed by cLIA in females **9 to 15** years of age

compared with females **20 to 26** years of age. The statistical criterion for noninferiority required that the lower bound of 2-sided 97.5% CI of GMT ratio (females 9 to 15 years of age vs. females 20 to 26 years of age) was >0.67 for each HPV type.

Stage II – Primary: To evaluate persistence of immune responses induced by the 9vHPV vaccine assessed by cLIA and IgG LIA in females 9 to 19 years of age.

*Table 2 Objectives and Endpoints in Stage II*

| Objective/Hypothesis | Endpoint |
|---|---|
| **Primary** | |
| • Objective: To evaluate persistence of immune responses induced by the 9vHPV vaccine in females 9 to 19 years of age. | • cLIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.<br>• IgG LIA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. |
| **Secondary** | |
| • Objective: To evaluate the safety of the 9vHPV vaccine in females 9 to 19 years of age based on the proportion of participants experiencing serious AEs. | • Participant experiencing serious AEs. |
| **Exploratory** | |
| • Objective: To summarize persistence of immune responses to the 9vHPV vaccine using PBNA in females 9 to 19 years of age. | • PBNA antibody titer and seropositivity to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. |

***Outcomes/endpoints***

The immunogenicity endpoints for the study were: serum HPV antibody levels (assessed as GMTs) and proportions of participants who seroconverted at Month 7 (Stage I); and GMTs and proportions of participants who were seropositive at Month 12, Month 24, Month 36, Month 48, and Month 60 (Stage II).

The primary immunoassay for the study was HPV-9 cLIA, which measured antibodies specific for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 in serum before and after vaccination with the 9vHPV vaccine.

The HPV-9 IgG LIA was used as a secondary measurement, complementary to the cLIA.

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

This study is an open-label study.

***Sample size***

Enrollment of participants was stratified into three age strata in Stage I. A total of 1990 participants was planned to be enrolled, with 690 participants 9 to 19 years of age, 650 participants 20 to 26 years of age and 650 participants 27 to 45 years of age.

- Within 9-19 years old stratum, approximately 2:1 allocation will be applied based on two age subgroups: 9-15 years old and 16-19 years old.

- Within 27-45 years old stratum, approximately 1:1 allocation will be applied based on two age subgroups: 27-35 years old and 36-45 years old.

The overall power to claim the study success in Stage I based on the dual-primary hypotheses is >0.999.

• Approximately an overall 99.1% power for H1 to demonstrate that females aged 9-19 years is non-inferior to females aged 20-26 years in terms of cLIA GMTs at 1 month post Dose 3 at an overall one-sided 1.25% alpha-level;

• Approximately an overall 92.9% power for H2 to demonstrate that females aged 27-45 years is non-inferior to females aged 20-26 years in terms of cLIA seroconversion percentages at 1 month post Dose 3 at an overall one-sided 1.25% alpha-level.

***Statistical Methods***

Analysis populations

*The Per-Protocol Immunogenicity Population*

The per-protocol immunogenicity (PPI) population was to serve as the primary population for analysis of immune responses to the 9vHPV vaccine. To be included in this population, participants must:

(1) Have received all 3 study vaccinations with the correct dose of the correct clinicalmaterial, and each vaccination visit must occur within the vaccination visit window

(2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, the participant must be seronegative to both HPV 6 and 11.

(3) Have provided post Dose 3 serum samples within the visit (i.e., Visit 10) window

(4) Have no other protocol violation that could interfere with the evaluation of participant's immune response to the study vaccine.

*All Type-Specific Naïve Participants with Serology Population*

A supportive immunogenicity analysis was to be carried out on the all type-specific naïve participants with serology (ANPS) population. To be included in this population, participants must:

(1) Have received all 3 study vaccinations.

(2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, the participant must be seronegative to both HPV 6 and 11.

(3) Have provided post Dose 3 serum samples.

Unlike the PPI population, the ANPS population included participants who met any exclusion criteria that were deemed to potentially interfere with the evaluation of immune responses to the 9vHPV vaccine. In addition, no day ranges on the timing of the vaccination and post Dose 3 serum sample collection was applied.

*Safety Analysis Populations*

The All Participants as Treated (APaT) population was to be used for the analysis of safety data in this study. The APaT population consisted of all participants who received at least one dose of study vaccination and had clinical follow-up for safety.

*Hypothesis Testing*

Stage I. Two dual-primary hypotheses, H1 and H2 shared a one-sided alpha level 0.025. The success criterion of the study was the success on either of the dual-primary hypotheses.

To test H1, the immune responses as measured by anti-HPV cLIA GMTs at 1 month post Dose 3 were to be analyzed separately for each of 9 HPV types. The statistical criterion for noninferiority required that the lower bound of two-sided 97.5% confidence interval of GMT ratio (9 to 19 years of age vs. 20 to 26 years of age) be greater than 0.67 for each HPV type. The primary hypothesis H1 was to be considered a success if the non-inferiority criteria for GMTs were met for all 9 HPV types in the comparisons between females 9 to 19 years of age vs. females 20 to 26 years of age.

For each HPV type, the hypothesis to be tested at $\alpha$=0.0125 level (1-sided) were

H0: GMT1/GMT2 ≤ 0.67

Ha: GMT1/GMT2 > 0.67

where GMT1 and GMT2 represented the GMTs at 1 month post Dose 3, in the 9 to19 year-old group and in the 20 to 26 year-old group, respectively. The point estimate of GMT was calculated by taking the anti-natural-logarithm of the arithmetic mean of the natural-logarithmtransformed anti-HPV titers. The test above was to be conducted using an ANOVA model with a response of log individual titers and a fixed effect for comparison group.

To test H2, cLIA seroconversion percentages at 1 month post Dose 3 was to be analyzed separately for each of 9 HPV types. The statistical criterion for non-inferiority required that the lower bound of two-sided 97.5% confidence interval of differences in seroconversion percentages (27 to 45 years of age minus 20 to 26 years of age) be greater than -5% for each HPV type. The primary hypothesis H2 was to be considered a success if the non-inferiority criteria for seroconversion percentages were met for all 9 HPV types in the comparisons between 27 to 45 years of age vs. 20 to 26 years of age.

The point estimate of seroconversion percentage for a particular HPV type was the ratio of the number of PPI-eligible participants for that particular HPV type who seroconverted to the relevant HPV type over the total number PPI-eligible participants for that particular HPV type.

For each HPV type, the hypothesis to be tested at $\alpha$=0.0125 level (1-sided) were:

H0: p1-p2 ≤ -0.05

Ha: p1-p2 > -0.05

where p1 was the proportion of participants who seroconverted by 1 month post Dose 3 in the 27 to 45 year-old group and p2 was the proportion of participants who seroconverted by 1 month post Dose 3 in the 20 to 26 year-old group.

The tests above were to be conducted using the method of Miettinen and Nurminen [16.1.12.4]. The statistical criterion for non-inferiority required that the lower bound of two-sided 97.5% confidence interval for the difference (27 to 45 years of age minus 20 to 26 years of age) in seroconversion percentages being greater than -5 percentage points for each HPV type. An adhoc analysis was performed to summarize the anti-HPV cLIA GMT ratios (27 to 45 years of age vs. 20 to 26 years of age) and related 95% CIs for each of the 9 vaccine HPV types using an ANOVA model.

Anti-HPV GMTs and seroconversion percentages measured by IgG LIA were to be summarized as secondary objective of immunogenicity.

PBNA results (GMTs and seroconversion percentages) were to be summarized as exploratory objective and were to be provided in a supplemental statistical report after the PBNA data of the Stage I are

available. HPV type-specific analysis of IgG LIA and PBNA was to be conducted in the corresponding HPV type-specific PPI population that was defined based on baseline cLIA anti-HPV serostatus.

*Table 3. Analysis Strategy in Stage I*

Table 9-2
Analysis Strategy for Immunogenicity Variables – Stage I

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach† | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| **Primary Objectives** | | | | |
| Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 (9-19yr vs. 20-26yr). (Each type will be tested separately.) | P | Point and 97.5% CI estimations as well as statistical testing will be performed by using an ANOVA model. | PPI | Observed data only |
| cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (27-45yr vs. 20-26yr). (Each type will be tested separately.) | P | Point and 97.5% CI estimations as well as statistical testing of binomial proportion are based on Miettinen & Nurminen method. | PPI | Observed data only |
| Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at Day 1 and 1 month post Dose 3 (9-19yr vs. 20-26yr). | S | Point and 95% CI estimations will be provided by t-distribution; no statistical testing and between group 95% CI will be given. | ANPS | Observed data only |
| cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (27-45yr vs. 20-26yr). | S | Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given. | ANPS | Observed data only |
| **Secondary Objectives** | | | | |
| cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (9-19yr vs. 20-26yr). (Each type will be tested separately.) | P | Point and 97.5% CI estimations as well as statistical testing of binomial proportion is based on Miettinen & Nurminen method. | PPI | Observed data only |
| Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 (9-15yr vs. 20-26yr). (Each type will be tested separately.) | P | Point and 97.5% CI estimations as well as statistical testing will be performed by using an ANOVA model. | PPI | Observed data only |
| cLIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3 (9-15yr vs. 20-26yr). | S | Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given. | PPI | Observed data only |

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach[†] | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|---|
| Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at Day 1 and 1 month post Dose 3 (27-45yr vs. 20-26yr). | S | Point and 95% CI estimations will be provided by t-distribution; no statistical testing and between group 95% CI will be given. | PPI | Observed data only |
| Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 IgG LIA GMTs at Day 1 and at 1 month post Dose 3. | S | Point and 95% CI estimations will be performed by t-distribution; no statistical testing and between group 95% CI will be given. | PPI | Observed data only |
| IgG LIA % seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post Dose 3. | S | Point and 95% CI estimations are based on exact method; no statistical testing and between group 95% CI will be given. | PPI | Observed data only |
| Impact of the time between Vaccination 2 and 3 on anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs at 1 month post Dose 3 by HPV type | S | Stepwise regression models | PPI | Observed data only |
| [†]P=Primary approach; S=Supportive approach.<br>ANPS = all type-specific naïve participants with serology; CI = confidence interval; GMT = geometric mean titer; PPI = per-protocol immunogenicity. | | | | |

*Multiplicity (Stage I)*

For the dual-primary hypotheses (H1 and H2), Bonferroni method was used to control overall one-sided type I error at level of 0.025. Each of the dual-primary hypotheses had a 0.0125 one-sided type I error. The study was to be successful if either H1 or H2 was met. If H1 was not met then no further testing (H3, H4) were to be completed.

Fix sequence testing strategy was used to control multiplicity between dual-primary hypothesis(H1) and secondary hypotheses (H3 and H4). The testing order was as follows: H1 (GMT, 9- 19yr vs. 20-26yr) was to be tested firstly and if H1 succeeded H3 (seroconversion percentages, 9-19yr vs. 20-26yr) was then to be tested; if H3 succeeded H4 (GMT, 9-15yr vs. 20-26yr) was to be tested. Each one was to be tested at a level of 0.0125. If anyone failed to reject null the subsequent ones would not be tested.

Furthermore, success was required on all 9 HPV types for hypotheses testing GMT and seroconversion percentages, so no multiplicity adjustment was needed to account for the multiple HPV types.

Stage II. The descriptive immunogenicity analyses were conducted on the PPI population, consisting of individuals who were seronegative to the appropriate HPV type(s) at Day 1, received all 3 vaccinations and had provided a post Dose-3 serology sample within a prespecified time frame, and had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine.

## Results

### *Participant flow*

*Table 4. Disposition of Participants through Stage I and II*

Table 10-1
Disposition of Participants
(All Enrolled Participants)
(Day 1 to Month 60)

| | 9 to 19 Years of Age | | 20 to 26 Years of Age | | 27 to 45 Years of Age | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Not enrolled | 39 | | 46 | | 90 | | 175 | |
| Participants in population | 690 | | 650 | | 650 | | 1,990 | |
| **Vaccinated at** | | | | | | | | |
| Vaccination 1 | 688 | (99.7) | 650 | (100.0) | 650 | (100.0) | 1,988 | (99.9) |
| Vaccination 2 | 683 | (99.0) | 647 | (99.5) | 644 | (99.1) | 1,974 | (99.2) |
| Vaccination 3 | 682 | (98.8) | 635 | (97.7) | 641 | (98.6) | 1,958 | (98.4) |
| **Status for Study Medication in Trial** | | | | | | | | |
| Started | 688 | | 650 | | 650 | | 1,988 | |
| Completed | 682 | (99.1) | 635 | (97.7) | 641 | (98.6) | 1,958 | (98.5) |
| Discontinued | 6 | (0.9) | 15 | (2.3) | 9 | (1.4) | 30 | (1.5) |
| Withdrawal By Parent/Guardian | 3 | (0.4) | 0 | (0.0) | 0 | (0.0) | 3 | (0.2) |
| Withdrawal By Subject | 3 | (0.4) | 15 | (2.3) | 9 | (1.4) | 27 | (1.4) |
| **Status for Trial Segment (Stage I)** | | | | | | | | |
| Entered | 690 | | 650 | | 650 | | 1,990 | |
| Completed | 682 | (98.8) | 635 | (97.7) | 641 | (98.6) | 1,958 | (98.4) |
| Discontinued | 8 | (1.2) | 15 | (2.3) | 9 | (1.4) | 32 | (1.6) |
| Withdrawal By Parent/Guardian | 3 | (0.4) | 0 | (0.0) | 0 | (0.0) | 3 | (0.2) |
| Withdrawal By Subject | 5 | (0.7) | 15 | (2.3) | 9 | (1.4) | 29 | (1.5) |
| **Status for Next Trial Segment (Stage II)** | | | | | | | | |
| Entered | 682 | | NA | | NA | | 682 | |
| Completed | 645 | (94.6) | NA | | NA | | 645 | (94.6) |
| Discontinued | 37 | (5.4) | NA | | NA | | 37 | (5.4) |
| Lost To Follow-Up | 12 | (1.8) | NA | | NA | | 12 | (1.8) |
| Withdrawal By Subject | 25 | (3.7) | NA | | NA | | 25 | (3.7) |

NA = Not applicable.

Source: [P024X01V503: adam-adsl; adpm; adex]

*Table 5 Stage I immunogenicity analysis populations*

Table 10-2
Participant Accounting for the Immunogenicity Analysis Populations by Age Group
(Day 1 to 1 Month Post Dose 3) (All Enrolled Participants)

| | 9 to 19 Years of Age (N=690) | 20 to 26 Years of Age (N=650) | 27 to 45 Years of Age (N=650) | Total (N=1990) |
|---|---|---|---|---|
| **Number of all enrolled participants** | **690** | **650** | **650** | **1990** |
| **Eligible for the PPI Analysis Related to:** | | | | |
| HPV 6/11 | 640 | 567 | 517 | 1724 |
| HPV 16 | 662 | 595 | 575 | 1832 |
| HPV 18 | 630 | 574 | 575 | 1779 |
| HPV 31 | 657 | 587 | 576 | 1820 |
| HPV 33 | 642 | 589 | 569 | 1800 |
| HPV 45 | 655 | 598 | 598 | 1851 |
| HPV 52 | 649 | 572 | 578 | 1799 |
| HPV 58 | 645 | 580 | 534 | 1759 |
| **Ineligible for the PPI Analysis Related to:** | | | | |
| HPV 6/11 | 50 | 83 | 133 | 266 |
| HPV 16 | 28 | 55 | 75 | 158 |
| HPV 18 | 60 | 76 | 75 | 211 |
| HPV 31 | 33 | 63 | 74 | 170 |
| HPV 33 | 48 | 61 | 81 | 190 |
| HPV 45 | 35 | 52 | 52 | 139 |
| HPV 52 | 41 | 78 | 72 | 191 |
| HPV 58 | 45 | 70 | 116 | 231 |
| **Eligible for the ANPS Analysis Related to:** | | | | |
| HPV 6/11 | 644 | 584 | 527 | 1755 |
| HPV 16 | 668 | 612 | 585 | 1865 |
| HPV 18 | 636 | 591 | 586 | 1813 |
| HPV 31 | 663 | 606 | 586 | 1855 |
| HPV 33 | 647 | 608 | 579 | 1834 |
| HPV 45 | 660 | 614 | 608 | 1882 |
| HPV 52 | 654 | 591 | 586 | 1831 |
| HPV 58 | 651 | 596 | 541 | 1788 |
| **Ineligible for the ANPS Analysis Related to:** | | | | |
| HPV 6/11 | 46 | 66 | 123 | 235 |
| HPV 16 | 22 | 38 | 65 | 125 |
| HPV 18 | 54 | 59 | 64 | 177 |
| HPV 31 | 27 | 44 | 64 | 135 |
| HPV 33 | 43 | 42 | 71 | 156 |
| HPV 45 | 30 | 36 | 42 | 108 |
| HPV 52 | 36 | 59 | 64 | 159 |
| HPV 58 | 39 | 54 | 109 | 202 |
| **Reason for Ineligibility[a]** | | | | |
| Received non-study vaccination[b] | 0 | 3 | 0 | 3 |
| Received immunosuppressives, IgG, or blood products | 4 | 13 | 9 | 26 |
| Has a history of a positive test for HPV and cervical intraepithelial neoplasia | 0 | 0 | 1 | 1 |
| 2nd or 3rd vaccination out of acceptable day range[c] | 1 | 2 | 1 | 4 |
| Did not complete the 3-dose regimen | 8 | 15 | 9 | 32 |
| Missing post dose 3 serology samples | 8 | 15 | 9 | 32 |
| Post dose 3 serology samples out of acceptable day range[c] | 1 | 1 | 0 | 2 |
| HPV 6 or 11 Positive by Serology at Day 1[d] | 39 | 52 | 115 | 206 |
| HPV 16 Positive by Serology at Day 1[d] | 14 | 24 | 57 | 95 |
| HPV 18 Positive by Serology at Day 1[d] | 46 | 44 | 55 | 145 |
| HPV 31 Positive by Serology at Day 1[d] | 19 | 31 | 56 | 106 |
| HPV 33 Positive by Serology at Day 1[d] | 35 | 30 | 62 | 127 |
| HPV 45 Positive by Serology at Day 1[d] | 22 | 21 | 33 | 76 |
| HPV 52 Positive by Serology at Day 1[d] | 29 | 45 | 56 | 130 |
| HPV 58 Positive by Serology at Day 1[d] | 31 | 42 | 102 | 175 |

[a]Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[b]Includes inactivated or recombinant vaccines received within 14 days of study vaccination or receipt of live vaccines within 21 days before study vaccination.
[c]Acceptable day ranges are provided in Schedule of Activities of the study protocol (Section 1.3).
[d]Applies only to the analysis populations for the respective HPV type(s).
N = Number of participants allocated to the respective age group.
ANPS =All type-specific naïve participants with serology; HPV = Human papillomavirus; PPI = Per-Protocol immunogenicity.
Source: [P024V503: adam-adsl; adpv]

*Table 6 Stage II Immunogenicity analysis population*

Table 10-2
Participant Accounting for the Immunogenicity Analysis Populations
(All Enrolled Participants in Stage II)

| | 9 to 19 Years of Age (N=682) |
|---|---|
| **Number of all enrolled participants** | **682** |
| **Eligible for the PPI Analysis Related to:** | |
| HPV 6/11 | 640 |
| HPV 16 | 662 |
| HPV 18 | 630 |
| HPV 31 | 657 |
| HPV 33 | 642 |
| HPV 45 | 655 |
| HPV 52 | 649 |
| HPV 58 | 645 |
| **Ineligible for the PPI Analysis Related to:** | |
| HPV 6/11 | 42 |
| HPV 16 | 20 |
| HPV 18 | 52 |
| HPV 31 | 25 |
| HPV 33 | 40 |
| HPV 45 | 27 |
| HPV 52 | 33 |
| HPV 58 | 37 |
| **Reason for Ineligibility[a]** | |
| Received immunosuppressives, IgG, or blood products | 4 |
| 2nd or 3rd vaccination out of acceptable day range[b] | 1 |
| Post dose 3 serology samples out of acceptable day range[b] | 1 |
| HPV 6 or 11 Positive by Serology at Day 1[c] | 38 |
| HPV 16 Positive by Serology at Day 1[c] | 14 |
| HPV 18 Positive by Serology at Day 1[c] | 46 |
| HPV 31 Positive by Serology at Day 1[c] | 19 |
| HPV 33 Positive by Serology at Day 1[c] | 35 |
| HPV 45 Positive by Serology at Day 1[c] | 22 |
| HPV 52 Positive by Serology at Day 1[c] | 28 |
| HPV 58 Positive by Serology at Day 1[c] | 31 |

[a]Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.
[b]Acceptable day ranges are provided in Schedule of Activities of the study protocol (Section 1.3).
[c]Applies only to the analysis populations for the respective HPV type(s).
N = Number of participants who entered Stage II; HPV = Human papillomavirus; PPI = Per-Protocol immunogenicity.

Source: [P024X01V503: adam-adsl; adpv]

***Recruitment***

| | |
|---|---|
| First Participant First Visit | 27-APR-2019 first participant first visit (Stage I)<br>05-MAY-2020 first participant first visit (Stage II) |
| Study Completion Date | 28-FEB-2025 last participant last visit (Stage II)<br>22-JUL-2025 last data available (Stage II) |

This study was conducted at 2 sites in China.

***Baseline data***

*Table 7 Stage I population baseline characteristics*

Table 10-3
Participant Characteristics by Age Group At Enrollment
(All Enrolled Participants)

| | 9 to 19 Years of Age | | 20 to 26 Years of Age | | 27 to 45 Years of Age | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Participants in population | 690 | | 650 | | 650 | | 1,990 | |
| **Sex** | | | | | | | | |
| Female | 690 | (100.0) | 650 | (100.0) | 650 | (100.0) | 1,990 | (100.0) |
| **Age (Years)** | | | | | | | | |
| Mean | 14.0 | | 23.1 | | 35.5 | | 24.0 | |
| SD | 3.0 | | 1.7 | | 5.1 | | 9.5 | |
| Median | 14.0 | | 23.0 | | 35.5 | | 23.0 | |
| Range | 9 to 19 | | 20 to 26 | | 27 to 45 | | 9 to 45 | |
| **Race** | | | | | | | | |
| Asian | 690 | (100.0) | 650 | (100.0) | 650 | (100.0) | 1,990 | (100.0) |
| **Weight (kg)** | | | | | | | | |
| Participants with data | 690 | | 650 | | 650 | | 1990 | |
| Mean | 47.0 | | 52.3 | | 54.9 | | 51.3 | |
| SD | 11.3 | | 8.1 | | 7.9 | | 9.8 | |
| Median | 47.3 | | 51.0 | | 54.2 | | 51.1 | |
| Range | 21.6 to 106.4 | | 34.1 to 86.8 | | 37.8 to 91.6 | | 21.6 to 106.4 | |
| **Height (cm)** | | | | | | | | |
| Participants with data | 690 | | 650 | | 650 | | 1990 | |
| Mean | 154.4 | | 158.2 | | 156.7 | | 156.4 | |
| SD | 9.5 | | 5.2 | | 5.4 | | 7.2 | |
| Median | 156.0 | | 158.0 | | 157.0 | | 157.0 | |
| Range | 123.0 to 177.0 | | 139.0 to 173.0 | | 140.5 to 175.0 | | 123.0 to 177.0 | |

Source: [P024V503: adam-adsl]

*Table 8 Stage II population baseline characteristics*

Table 10-3
Participant Characteristics at Enrollment
(All Enrolled Participants in Stage II)

| | 9 to 19 Years of Age | |
|---|---|---|
| | n | (%) |
| Participants in population | 682 | |
| **Sex** | | |
| Female | 682 | (100.0) |
| **Age (Years)** | | |
| Mean | 14.0 | |
| SD | 3.0 | |
| Median | 14.0 | |
| Range | 9 to 19 | |
| **Race** | | |
| Asian | 682 | (100.0) |
| **Ethnicity** | | |
| Not Hispanic Or Latino | 682 | (100.0) |
| **Weight (kg)** | | |
| Participants with data | 682 | |
| Mean | 47.0 | |
| SD | 11.3 | |
| Median | 47.3 | |
| Range | 21.6 to 106.4 | |
| **Height (cm)** | | |
| Participants with data | 682 | |
| Mean | 154.4 | |
| SD | 9.4 | |
| Median | 156.0 | |
| Range | 123.0 to 177.0 | |
| SD=Standard deviation. | | |

Source: [P024X01V503: adam-adsl]

***Number analysed***

- Stage I: A total of 1990 participants (9 to 19 years, n=690; 20 to 26 years, n=650; 27 to 45 years: n=650) were enrolled to receive 3 doses of 9vHPV vaccine at Day 1, Month 2, and Month 6, and 1988 received at least 1 dose of study vaccination. Of those, 1958 (98.5%) completed the 3-dose regimen. Thirty participants (1.5%) discontinued study vaccination, the majority (n=27) due to withdrawal by subject. No participants discontinued from Stage I due to an AE.
- Stage II: A total of 682 participants in the 9 to 19 year old group completed the 3-dose regimen of the 9vHPV vaccine during Stage I and all entered Stage II. Of these, 645 (94.6%) participants completed Stage II. There were 37 participants (5.4%) who discontinued early from Stage II, due to withdrawal by subject (25 participants [3.7%]) or lost to follow-up (12 participants [1.8%]).

***Efficacy results***

**Stage I: Immunogenicity Bridging From Females 9 to 19 Years of Age to Females 20 to 26 Years of Age**

Primary Immunogenicity Analyses in the PPI Population:

The cLIA GMT ratios (9 to 19 year old group vs. 20 to 26 year old group) at 1 month post Dose 3 ranged from 1.27 to 1.48 depending on the HPV type. The lower bound of 97.5% CI of the GMT ratios

ranged from 1.16 to 1.33, exceeding the prespecified noninferiority margin of 0.67 for all vaccine HPV types. Therefore, noninferiority of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs in females 9 to 19 years of age compared with females 20 to 26 years of age at Month 7 was demonstrated.

*Table 9. Non-Inferiority analysis for cLIA GMTs in 9-19 yo. compared to 20-26 yo.*

Statistical Analysis of Non-Inferiority of cLIA Geometric Mean Titers at 1 Month Post Dose 3
Comparing 9-19 years old girls with 20-26 years old women
(Per-Protocol Immunogenicity Population)

| Assay(cLIA) | 9 to 19 Years of Age (N=688) | | 20 to 26 Years of Age (N=650) | | GMT Ratio(97.5% CI) 9-19yr/20-26yr | p-Value for Non-Inferiority* |
|---|---|---|---|---|---|---|
| | n | GMT (mMU/mL) | n | GMT (mMU/mL) | | |
| Anti-HPV 6 | 640 | 1129.7 | 567 | 861.7 | 1.31 (1.20,1.43) | <0.0001 |
| Anti-HPV 11 | 640 | 926.7 | 567 | 702.6 | 1.32 (1.20,1.45) | <0.0001 |
| Anti-HPV 16 | 662 | 4972.3 | 595 | 3723.7 | 1.34 (1.22,1.47) | <0.0001 |
| Anti-HPV 18 | 630 | 1438.4 | 574 | 1031.6 | 1.39 (1.25,1.55) | <0.0001 |
| Anti-HPV 31 | 657 | 1161.5 | 587 | 821.9 | 1.41 (1.28,1.56) | <0.0001 |
| Anti-HPV 33 | 642 | 664.3 | 589 | 497.5 | 1.34 (1.21,1.47) | <0.0001 |
| Anti-HPV 45 | 655 | 442.9 | 598 | 299.1 | 1.48 (1.33,1.65) | <0.0001 |
| Anti-HPV 52 | 649 | 505.9 | 572 | 397.8 | 1.27 (1.16,1.40) | <0.0001 |
| Anti-HPV 58 | 645 | 725.3 | 580 | 535.9 | 1.35 (1.23,1.49) | <0.0001 |

*For the null hypothesis that GMT (9-19 yr)/GMT(20-26 yr) ≤ 0.67, a p-value <0.0125 supports a conclusion that the type-specific anti-HPV cLIA GMT in girls aged 9-19 years is non-inferior to that in young women aged 20-26 years at 1 month post dose 3.
The estimated GMT ratios, associated CIs, and p-values are calculated using an ANOVA model with a response of log individual titers and a fixed effect for comparison group.
N = Number of participants in the indicated age group who have received at least one dose of the 9vHPV vaccine.
n = Number of participants contributing to the analysis.
ANOVA = Analysis of variance; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; 9vHPV = 9-valent human papillomavirus.

Source: [P024V503: adam-adsl: adimm]

The cLIA seroconversion percentages at 1 month post Dose 3 were 100% for all vaccine HPV types in females aged 27 to 45 years; 100% for all vaccine HPV types except for HPV18 (99.8% seroconversion) in females aged 20 to 26 years. The lower bound of 97.5% CI for the difference in cLIA seroconversion percentages ranged from -1.0 to 0.7 exceeding the prespecified noninferiority margin of -5% for all vaccine HPV types. Therefore, noninferiority of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 seroconversion percentages in females 27 to 45 years of age compared with females 20 to 26 years of age at Month 7 was demonstrated.

*Table 10. Non-Inferiority Analysis of Seroconversion Percentage in 27-45 yo. compared to 20-26 yo.*

Statistical Analysis of Non-Inferiority of cLIA Seroconversion Percentages at 1 Month Post Dose 3
Comparing 27-45 years old women with 20-26 years old women
(Per-Protocol Immunogenicity Population)

| Anti-HPV Response ≥ Cuoff Value | 27 to 45 Years of Age (N=650) | | | 20 to 26 Years of Age (N=650) | | | Difference of Seroconversion[a] Percentages(%) (97.5% CI) (27-45yr)-(20-26yr) | p-Value for Non-inferiority[b] |
|---|---|---|---|---|---|---|---|---|
| | n | m | Seroconversion[a] Percentages (%) | n | m | Seroconversion[a] Percentages (%) | | |
| Anti-HPV 6 ≥ 50 mMU/mL | 517 | 517 | 100.0 | 567 | 567 | 100.0 | 0.0 (-1.0, 0.9) | <0.0001 |
| Anti-HPV 11 ≥ 29 mMU/mL | 517 | 517 | 100.0 | 567 | 567 | 100.0 | 0.0 (-1.0, 0.9) | <0.0001 |
| Anti-HPV 16 ≥ 41 mMU/mL | 575 | 575 | 100.0 | 595 | 595 | 100.0 | 0.0 (-0.9, 0.8) | <0.0001 |
| Anti-HPV 18 ≥ 59 mMU/mL | 575 | 575 | 100.0 | 574 | 573 | 99.8 | 0.2 (-0.7, 1.2) | <0.0001 |
| Anti-HPV 31 ≥ 29 mMU/mL | 576 | 576 | 100.0 | 587 | 587 | 100.0 | 0.0 (-0.9, 0.8) | <0.0001 |
| Anti-HPV 33 ≥ 22 mMU/mL | 569 | 569 | 100.0 | 589 | 589 | 100.0 | 0.0 (-0.9, 0.8) | <0.0001 |
| Anti-HPV 45 ≥ 15 mMU/mL | 598 | 598 | 100.0 | 598 | 598 | 100.0 | 0.0 (-0.8, 0.8) | <0.0001 |
| Anti-HPV 52 ≥ 20 mMU/mL | 578 | 578 | 100.0 | 572 | 572 | 100.0 | 0.0 (-0.9, 0.9) | <0.0001 |
| Anti-HPV 58 ≥ 15 mMU/mL | 534 | 534 | 100.0 | 580 | 580 | 100.0 | 0.0 (-0.9, 0.9) | <0.0001 |

[a]Seroconversion was defined as changing serostatus from seronegative at baseline to seropositive at 1 month post Dose 3. Cutoff values for HPV seropositivity are ≥50, 29, 41, 59, 29, 22, 15, 20, and 15 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.
[b]For the null hypothesis that p(27-45)-p(20-26) ≤ -5%, a p-value <0.0125 supports a conclusion that the type-specific anti-HPV cLIA seroconversion percentage in girls aged 27-45 years is non-inferior to that in young women aged 20-26 years.
The estimated differences in seroconversion percentages, associated CIs, and p-values are calculated using Miettinen & Nurminen method.
N = Number of participants in the indicated age group who have received at least one dose of the 9vHPV vaccine.
n = Number of participants contributing to the analysis. m= Number of participants with seropositivity. Percent is calculated as 100*(m/n).
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; 9vHPV = 9-valent human papillomavirus.

Source: [P024V503: adam-adsl; adimm]

Based on these results, efficacy of the 9vHPV vaccine in Chinese females 9 to 19 years of age and 27 to 45 years of age was inferred.

Key Secondary Immunogenicity Analyses in the PPI Population:

The cLIA seroconversion percentages at 1 month post Dose 3 were 100% for all vaccine HPV types in females aged 9 to 19 years; 100% for all vaccine HPV types except for HPV 18 (99.8% seroconversion) in females aged 20 to 26 years. The lower bound of 97.5% CI for the difference in cLIA seroconversion percentages ranged from -0.8 to 0.6 exceeding the prespecified noninferiority margin of -5% for all vaccine HPV types. Therefore, noninferiority of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA seroconversion percentages in females 9 to 19 year of age versus females 20 to 26 year of age at Month 7 was demonstrated.

*Table 11 Non-Inferiority analysis for Seroconversion Percentage in 9-19 yo. compared to 20-26 yo.*

Table 11-3
Statistical Analysis of Non-Inferiority of cLIA Seroconversion Percentages at 1 Month Post Dose 3
Comparing 9-19 years old girls with 20-26 years old women
(Per-Protocol Immunogenicity Population)

| Anti-HPV Response ≥ Cuoff Value | 9 to 19 Years of Age (N=688) | | | 20 to 26 Years of Age (N=650) | | | Difference of Seroconversion[a] Percentages(%) (97.5% CI) (9-19yr)-(20-26yr) | p-Value for Non-inferiority[b] |
|---|---|---|---|---|---|---|---|---|
| | n | m | Seroconversion[a] Percentages (%) | n | m | Seroconversion[a] Percentages (%) | | |
| Anti-HPV 6 ≥ 50 mMU/mL | 640 | 640 | 100.0 | 567 | 567 | 100.0 | 0.0 (-0.8, 0.9) | <0.0001 |
| Anti-HPV 11 ≥ 29 mMU/mL | 640 | 640 | 100.0 | 567 | 567 | 100.0 | 0.0 (-0.8, 0.9) | <0.0001 |
| Anti-HPV 16 ≥ 41 mMU/mL | 662 | 662 | 100.0 | 595 | 595 | 100.0 | 0.0 (-0.8, 0.8) | <0.0001 |
| Anti-HPV 18 ≥ 59 mMU/mL | 630 | 630 | 100.0 | 574 | 573 | 99.8 | 0.2 (-0.6, 1.2) | <0.0001 |
| Anti-HPV 31 ≥ 29 mMU/mL | 657 | 657 | 100.0 | 587 | 587 | 100.0 | 0.0 (-0.8, 0.8) | <0.0001 |
| Anti-HPV 33 ≥ 22 mMU/mL | 642 | 642 | 100.0 | 589 | 589 | 100.0 | 0.0 (-0.8, 0.8) | <0.0001 |
| Anti-HPV 45 ≥ 15 mMU/mL | 655 | 655 | 100.0 | 598 | 598 | 100.0 | 0.0 (-0.8, 0.8) | <0.0001 |
| Anti-HPV 52 ≥ 20 mMU/mL | 649 | 649 | 100.0 | 572 | 572 | 100.0 | 0.0 (-0.8, 0.9) | <0.0001 |
| Anti-HPV 58 ≥ 15 mMU/mL | 645 | 645 | 100.0 | 580 | 580 | 100.0 | 0.0 (-0.8, 0.9) | <0.0001 |

[a]Seroconversion was defined as changing serostatus from seronegative at baseline to seropositive at 1 month post Dose 3. Cutoff values for HPV seropositivity are ≥50, 29, 41, 59, 29, 22, 15, 20, and 15 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively.
[b]For the null hypothesis that p(9-19)-p(20-26) ≤ -5%, a p-value <0.0125 supports a conclusion that the type-specific anti-HPV cLIA seroconversion percentage in girls aged 9-19 years is non-inferior to that in young women aged 20-26 years.
The estimated differences in seroconversion percentages, associated CIs, and p-values are calculated using Miettinen & Nurminen method.
N = Number of participants in the indicated age group who have received at least one dose of the 9vHPV vaccine.
n = Number of participants contributing to the analysis. m= Number of participants with seropositivity. Percent is calculated as 100*(m/n).
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; 9vHPV = 9-valent human papillomavirus.

Source: [P024V503: adam-adsl: adimm]

The cLIA GMT ratios (9 to 15 year old group vs. 20 to 26 year old group) at 1 month post Dose 3 ranged from 1.35 to 1.64 depending on the HPV type. The lower bound of 97.5% CI of the GMT ratios ranged from 1.21 to 1.46, exceeding the prespecified noninferiority margin of 0.67 for all vaccine HPV types. Therefore, noninferiority of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA GMTs in females 9 to 15 years of age compared with females 20 to 26 years of age at Month 7 was demonstrated.

*Table 12. Non-Inferiority analysis for cLIA GMTs 9-15 yo. compared to 20-26 yo.*

Table 11-4
Statistical Analysis of Non-Inferiority of cLIA Geometric Mean Titers at 1 Month Post Dose 3
Comparing 9-15 years old girls with 20-26 years old women
(Per-Protocol Immunogenicity Population)

| Assay(cLIA) | 9 to 15 Years of Age (N=458) | | 20 to 26 Years of Age (N=650) | | GMT Ratio(97.5% CI) 9-15yr/20-26yr | p-Value for Non-Inferiority[a] |
|---|---|---|---|---|---|---|
| | n | GMT (mMU/mL) | n | GMT (mMU/mL) | | |
| Anti-HPV 6 | 426 | 1201.1 | 567 | 861.7 | 1.39 (1.27,1.53) | <0.0001 |
| Anti-HPV 11 | 426 | 981.6 | 567 | 702.6 | 1.40 (1.26,1.55) | <0.0001 |
| Anti-HPV 16 | 441 | 5279.6 | 595 | 3723.7 | 1.42 (1.28,1.57) | <0.0001 |
| Anti-HPV 18 | 422 | 1582.4 | 574 | 1031.6 | 1.53 (1.37,1.72) | <0.0001 |
| Anti-HPV 31 | 436 | 1253.1 | 587 | 821.9 | 1.52 (1.37,1.70) | <0.0001 |
| Anti-HPV 33 | 432 | 699.6 | 589 | 497.5 | 1.41 (1.27,1.56) | <0.0001 |
| Anti-HPV 45 | 437 | 490.5 | 598 | 299.1 | 1.64 (1.46,1.84) | <0.0001 |
| Anti-HPV 52 | 430 | 535.1 | 572 | 397.8 | 1.35 (1.21,1.49) | <0.0001 |
| Anti-HPV 58 | 429 | 771.5 | 580 | 535.9 | 1.44 (1.29,1.60) | <0.0001 |

[a]For the null hypothesis that GMT (9-15 yr)/GMT(20-26 yr) ≤ 0.67, a p-value <0.0125 supports a conclusion that the type-specific anti-HPV cLIA GMT in girls aged 9-15 years is non-inferior to that in young women aged 20-26 years at 1 month post dose 3.
The estimated GMT ratios, associated CIs, and p-values are calculated using an ANOVA model with a response of log individual titers and a fixed effect for comparison group.
N = Number of participants in the indicated age group who have received at least one dose of the 9vHPV vaccine.
n = Number of participants contributing to the analysis.
ANOVA = Analysis of variance; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; 9vHPV = 9-valent human papillomavirus.

Source: [P024V503: adam-adsl; adimm]

**Stage II: Persistence of Immune Responses Through Month 60 in Females 9 to 19 Years of Age**

Primary Immunogenicity Analyses in the PPI Population:

Among Stage II participants, anti-HPV cLIA GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 peaked at 1 month post Dose 3, declined sharply through Month 12, and decreased gradually from Month 12 through Month 60. The cLIA seropositivity percentages for all 9 vaccine HPV types were 100% at Month 7, remained high from Month 12 through Month 60, and ranged from 89.7% to 98.9% at Month 60, depending on the HPV type.

*Table 13. cLIA Immune Responses in 9-19 yo. Up to 60 months post vaccination.*

| | 9 to 19 Years of Age (N=682) | | | |
|---|---|---|---|---|
| Assay (cLIA) Study Timepoint | n | GMT (mMU/mL) (95% CI) | m | Seropositivity Percentages (%) (95% CI) |
| Anti-HPV 6 | | | | |
| Day 1 | 640 | 23.9 (23.5, 24.3) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 640 | 1129.7 (1069.8, 1193.0) | 640 | 100.0 (99.4, 100.0) |
| Month 12 | 638 | 420.3 (393.3, 449.1) | 635 | 99.5 (98.6, 99.9) |
| Month 24 | 636 | 210.2 (196.4, 225.0) | 613 | 96.4 (94.6, 97.7) |
| Month 36 | 616 | 172.6 (161.6, 184.4) | 538 | 87.3 (84.5, 89.9) |
| Month 48 | 616 | 170.3 (158.9, 182.6) | 580 | 94.2 (92.0, 95.9) |
| Month 60 | 604 | 154.2 (143.5, 165.6) | 559 | 92.5 (90.2, 94.5) |
| Anti-HPV 11 | | | | |
| Day 1 | 640 | 16.1 (16.0, 16.1) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 640 | 926.7 (876.4, 979.8) | 640 | 100.0 (99.4, 100.0) |
| Month 12 | 638 | 341.9 (320.1, 365.3) | 638 | 100.0 (99.4, 100.0) |
| Month 24 | 636 | 172.2 (160.7, 184.5) | 625 | 98.3 (96.9, 99.1) |
| Month 36 | 616 | 136.5 (127.6, 146.0) | 582 | 94.5 (92.4, 96.1) |
| Month 48 | 616 | 123.4 (115.0, 132.3) | 591 | 95.9 (94.1, 97.4) |
| Month 60 | 604 | 111.3 (103.5, 119.6) | 565 | 93.5 (91.3, 95.4) |
| Anti-HPV 16 | | | | |
| Day 1 | 662 | 20.3 (20.2, 20.4) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 662 | 4972.3 (4696.9, 5263.9) | 662 | 100.0 (99.4, 100.0) |
| Month 12 | 660 | 1748.7 (1636.7, 1868.3) | 660 | 100.0 (99.4, 100.0) |
| Month 24 | 658 | 774.8 (717.2, 837.1) | 652 | 99.1 (98.0, 99.7) |
| Month 36 | 637 | 600.5 (554.3, 650.6) | 618 | 97.0 (95.4, 98.2) |
| Month 48 | 636 | 612.6 (568.8, 659.8) | 630 | 99.1 (98.0, 99.7) |
| Month 60 | 624 | 541.7 (502.0, 584.5) | 617 | 98.9 (97.7, 99.5) |
| Anti-HPV 18 | | | | |
| Day 1 | 630 | 31.7 (31.1, 32.4) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 630 | 1438.4 (1349.0, 1533.6) | 630 | 100.0 (99.4, 100.0) |
| Month 12 | 628 | 472.2 (440.6, 506.1) | 622 | 99.0 (97.9, 99.6) |
| Month 24 | 627 | 226.9 (211.8, 243.0) | 600 | 95.7 (93.8, 97.1) |
| Month 36 | 609 | 178.0 (166.3, 190.5) | 490 | 80.5 (77.1, 83.5) |
| Month 48 | 607 | 151.9 (140.1, 164.8) | 560 | 92.3 (89.8, 94.3) |
| Month 60 | 597 | 132.9 (122.5, 144.1) | 539 | 90.3 (87.6, 92.5) |
| Anti-HPV 31 | | | | |
| Day 1 | 657 | 11.6 (11.4, 11.8) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 657 | 1161.5 (1093.2, 1234.2) | 657 | 100.0 (99.4, 100.0) |
| Month 12 | 655 | 403.5 (375.6, 433.5) | 651 | 99.4 (98.4, 99.8) |
| Month 24 | 653 | 205.3 (190.4, 221.4) | 640 | 98.0 (96.6, 98.9) |
| Month 36 | 633 | 166.9 (154.7, 180.0) | 573 | 90.5 (88.0, 92.7) |
| Month 48 | 632 | 165.6 (153.2, 178.9) | 621 | 98.3 (96.9, 99.1) |

| | | | | |
|---|---|---|---|---|
| Month 60 | 620 | 147.1 (135.9, 159.2) | 605 | 97.6 (96.0, 98.6) |
| Anti-HPV 33 | | | | |
| Day 1 | 642 | 10.3 (10.1, 10.6) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 642 | 664.3 (626.3, 704.7) | 642 | 100.0 (99.4, 100.0) |
| Month 12 | 640 | 237.7 (221.8, 254.8) | 637 | 99.5 (98.6, 99.9) |
| Month 24 | 638 | 120.4 (112.2, 129.2) | 625 | 98.0 (96.5, 98.9) |
| Month 36 | 618 | 95.1 (88.6, 102.1) | 586 | 94.8 (92.8, 96.4) |
| Month 48 | 617 | 87.9 (81.4, 94.9) | 601 | 97.4 (95.8, 98.5) |
| Month 60 | 605 | 79.0 (73.1, 85.3) | 582 | 96.2 (94.4, 97.6) |

Summary of cLIA Immune Responses by Visit
(Per-Protocol Immunogenicity Population Entered into Stage II)

| | 9 to 19 Years of Age (N=682) | | | |
|---|---|---|---|---|
| Assay (cLIA) Study Timepoint | n | GMT (mMU/mL) (95% CI) | m | Seropositivity Percentages (%) (95% CI) |
| Anti-HPV 45 | | | | |
| Day 1 | 655 | 8.6 (8.5, 8.6) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 655 | 442.9 (415.0, 472.7) | 655 | 100.0 (99.4, 100.0) |
| Month 12 | 653 | 144.0 (133.4, 155.3) | 646 | 98.9 (97.8, 99.6) |
| Month 24 | 651 | 72.1 (66.8, 77.8) | 630 | 96.8 (95.1, 98.0) |
| Month 36 | 631 | 56.9 (52.8, 61.4) | 536 | 84.9 (81.9, 87.6) |
| Month 48 | 630 | 53.5 (49.4, 57.9) | 584 | 92.7 (90.4, 94.6) |
| Month 60 | 619 | 48.3 (44.5, 52.4) | 555 | 89.7 (87.0, 91.9) |
| Anti-HPV 52 | | | | |
| Day 1 | 649 | 9.4 (9.2, 9.5) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 649 | 505.9 (478.4, 535.0) | 649 | 100.0 (99.4, 100.0) |
| Month 12 | 647 | 187.6 (175.8, 200.2) | 645 | 99.7 (98.9, 100.0) |
| Month 24 | 645 | 97.5 (91.3, 104.2) | 625 | 96.9 (95.3, 98.1) |
| Month 36 | 626 | 78.1 (73.2, 83.4) | 544 | 86.9 (84.0, 89.4) |
| Month 48 | 625 | 75.3 (70.5, 80.4) | 605 | 96.8 (95.1, 98.0) |
| Month 60 | 613 | 68.6 (64.1, 73.3) | 584 | 95.3 (93.3, 96.8) |
| Anti-HPV 58 | | | | |
| Day 1 | 645 | 8.2 (8.1, 8.3) | 0 | 0.0 (0.0, 0.6) |
| Month 7 | 645 | 725.3 (685.6, 767.4) | 645 | 100.0 (99.4, 100.0) |
| Month 12 | 643 | 272.5 (255.5, 290.7) | 643 | 100.0 (99.4, 100.0) |
| Month 24 | 641 | 125.8 (117.0, 135.3) | 628 | 98.0 (96.6, 98.9) |
| Month 36 | 620 | 100.9 (93.9, 108.5) | 559 | 90.2 (87.5, 92.4) |
| Month 48 | 619 | 97.1 (90.5, 104.2) | 610 | 98.5 (97.3, 99.3) |
| Month 60 | 608 | 86.8 (80.6, 93.4) | 595 | 97.9 (96.4, 98.9) |

The estimated GMTs and associated CIs are calculated using t-distribution.

The seropositivity percentages and associated 95% CIs are calculated using the exact method.

The seropositivity percentage represents proportion of participants with below anti-HPV serum levels for HPV types HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58: ≥50, 29, 41, 59, 29, 22, 15, 20 and 15 mMU/mL, respectively, for timepoints before and at Month 24 (Visit 12); ≥65, 37, 79, 85, 46, 26, 21, 30 and 31 mMU/mL, respectively, for timepoints at Month 36 (Visit 13); and ≥34, 25, 32, 26, 15, 10, 10, 14 and 10 mMU/mL, respectively, for timepoints at Month 48 (Visit 14) and after.

N = Number of participants who have received 3 doses of the 9vHPV vaccine and entered the Stage II.

n = Number of participants contributing to the analysis. m= Number of participants with seropositivity to the relevant HPV type(s). Percent is calculated as 100*(m/n).

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; 9vHPV = 9-valent human papillomavirus.

Source: [P024X01V503: adam-adsl; adimm]

Consistent with the results of cLIA, anti-HPV IgG LIA GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 peaked at Month 7, declined sharply through Month 12, and decreased gradually from Month 12 through Month 60. The IgG LIA seropositivity for all 9 vaccine HPV types were 100% at Month 7,

remained high from Month 12 through Month 60, and ranged from 97.5% to 100% at Month 60, depending on the HPV type.

***Safety results***

Safety endpoints used to evaluate the safety and tolerability of the 9vHPV vaccine included:

- Stage I: proportions of participants with injection-site and systemic AEs from Day 1 through Day 8 following any study vaccination, and systemic AEs from Day 1 through Day 31 following any study vaccination. SAEs were reported throughout the duration of the study.
- Stage II: SAEs were reported throughout the duration of the study.

Safety analysis was conducted in the APaT population, which consisted of all participants who received at least 1 dose of study vaccination and had clinical follow-up for safety.

Adverse Events

*Injection-site Adverse Events*

Overall, 43.2% of participants in the 9 to 19 year old group, 49.7% in the 20 to 26 year old group, and 43.1% in the 27 to 45 year old group reported at least 1 injection-site AE from Days 1 to 8 following any vaccination visit. The most common injection-site AE during Days 1 to 8 following any vaccination visit was injection site pain across all age groups (39.1% of participants in the 9 to 19 year old group, 44.5% in the 20 to 26 year old group, and 39.1% in the 27 to 45 year old group).

The majority of injection-site AEs from Days 1 to 8 following any vaccination visit were mild to moderate in intensity across all age groups. The majority of injection-site erythema and swelling were 0 to ≤1 inch in maximum size across all age groups. Severe injection-site AEs from Day 1 to Day 8 following any vaccination were reported in 8 (1.2%) participants in the 9 to 19 year old group, and 9 (1.4%) participants in each of the 20 to 26 year old group and the 27 to 45 year old group.

Similar results were observed for all injection-site AEs reported during Day 1 to Day 31 following any vaccination. During Day 9 to Day 31 following any vaccination, few (<1%) participants reported injection-site erythema or swelling and the majority of these AEs were mild in intensity.

*Systemic Adverse Events*

A total of 50.9% of participants in the 9 to 19 year old group, 57.1% in the 20 to 26 year old group, and 43.4% in the 27 to 45 year old group experienced at least 1 systemic AE from Days 1 to 31 following any vaccination visit. The most common systemic AE (incidence ≥10% in any age group) was pyrexia across all age groups (25.0% in the 9 to 19 year old group, 26.9% in the 20 to 26 year old group, and 13.1% in the 27 to 45 year old group).

A total of 27.3% of participants in the 9 to 19 year old group, 33.4% of participants in the 20 to 26 year old group, and 17.8% of participants in the 27 to 45 year old group reported vaccine-related systemic AEs from Days 1 to 31 following any vaccination visit. The most common vaccine related systemic AE (incidence ≥10% in any age group) was pyrexia (22.1% in the 9 to 19 year old group, 25.5% in the 20 to 26 year old group, and 12.0% in the 27 to 45 year old group).

The majority of systemic AEs reported from Day 1 to Day 31 following any vaccination were mild to moderate in intensity across all age groups. Severe systemic AEs were reported in 3 participants (0.2%): 2 participants in the 20 to 26 year old group, and 1 participant in the 27 to 45 year old group.

*Maximum Temperatures*

The distribution of maximum temperatures (axillary or axillary equivalent) reported from Day 1 to Day 8 following any vaccination analyzed using MSD scale were generally similar across age groups. Approximately 87% of participants reported maximum temperature of <37.2°C.

*Serious Adverse Events*

During the entire study, no deaths were reported.

A total of 41 participants reported SAEs during Stage I, and 10 participants experienced SAEs during Stage II. In addition, 2 participants had SAEs that occurred during Stage I but were reported after the study entered Stage II. All SAEs resolved except for 1 SAE of facial bones fracture, which occurred during Stage I and resolved with sequalae. None were considered vaccine related.

There were no discontinuations from study vaccination due to an AE.

Summary of Safety Results

- The overall proportions of participants with injection-site AEs and systemic AEs were generally comparable across all age groups.
- The most common injection-site AE was injection-site pain, and the most common systemic AE was pyrexia.
- The majority of injection-site AEs and systemic AEs were mild to moderate in intensity.
- No vaccine-related SAEs were reported. No participants died during the study. No participant discontinued the study vaccination due to AEs.

### 2.3.3. Discussion on clinical aspects

The results of V503-024 Stage I demonstrated noninferiority of the serum antibody response generated by the 9vHPV vaccine for all HPV types in Chinese females 9 to 19 years of age and 27 to 45 years of age, compared with females 20 to 26 years of age (a population in which efficacy was previously established in a global efficacy study).

Administration of a 3-dose regimen of the 9vHPV vaccine to Chinese females 9 to 19 years of age induces anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses that generally persist through 5 years postvaccination 1 as observed in Stage II part of the study.

Based on these results, efficacy of the 9vHPV vaccine in Chinese females 9 to 19 years of age and 27 to 45 years of age is inferred. The data in this application are consistent with prior findings, demonstrating immunogenicity of the 9vHPV vaccine in young adolescents and women aged 27 to 45 years.

Administration of a 3-dose regimen of the 9vHPV vaccine to Chinese females 9 to 45 years of age was generally well tolerated through 5 years postvaccination 1. The safety profile in this study did not reveal any new findings compared with previous clinical and post licensure studies of the 9vHPV vaccine. There were no safety findings that would indicate any change to the safety profile of the 9vHPV vaccine, therefore no changes to the current EU product information are proposed based on the results presented.

# 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.