14 November 2024
EMA/557242/2024
Human Medicines Division

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

Gardasil

Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinat, adosrbed)

Procedure no.: EMEA/H/C/000703/P46/091

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	16 Sep 2024	16 Sep 2024
☐	CHMP Rapporteur Assessment Report	21 Oct 2024	21 Oct 2024
☐	CHMP members comments	04 Nov 2024	04 Nov 2024
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2024	n/a
☒	CHMP adoption of conclusions:	14 Nov 2024	14 Nov 2024

Table of contents

1. Introduction

On September 2, 2024, the MAH submitted a completed paediatric study for Gardasil, 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 the studies P213V501 (base stage) – A Phase 3 Open-Label Clinical Trials to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years, and P213X01V501 (extension stage) are stand-alone studies and were not part of EU paediatric investigation plan.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for:

- **P213V501** (base stage) - A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years.
- **P213X01V501** (extension stage) - A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years.

Clinical study reports and clinical overview were submitted.

2.3.2. Clinical studies

P213V501

A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years.

Description

Base Stage (Day 1 through Month 7), a single-site, open-label, immunogenicity, safety and tolerability study of qHPV vaccine in 9 to 19 years old and 20 to 26 years old Chinese female participants.

Methods

Participants enrolled in this study were allocated by non-random assignment for a 3-dose regimen of qHPV vaccine at day 1, month 2 and month 6.

Study participants

383 Chinese girls aged 9-19 years and 383 aged 20-26 years.

Treatments

All enrolled participants received one dose (0,5 mL) of qHPV vaccine under open-label conditions at the Day 1, Month 2, and Month 6 visits, respectively. Each dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Objectives

Primary Objective, Base Stage:

- To demonstrate that administration of a 3-dose regimen of V501 induces noninferior GMTs for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18 in girls aged 9 to 19 years compared to young women aged 20 to 26 years.

  Hypothesis (H1): 3-dose regimen of V501 induces noninferior immune responses in girls aged 9 to 19 years who are seronegative at Day 1 to the relevant HPV type(s) compared to young women aged 20 to 26 years who are seronegative at Day 1 to the relevant HPV type(s), as measured by anti-HPV 6, 11, 16, and 18 GMTs at 1 month post Dose 3.

  Endpoint: Competitive Luminex immunoassay (cLIA) GMTs to each of HPV 6, 11, 16, and 18 at 1 month post dose 3.

Key Secondary Objective, Base Stage:

- To demonstrate that a 3-dose regimen of V501 induces noninferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, and 18 in girls aged 9 to 19 years compared to young women 20 to 26 years.

  Hypothesis (H2): 3-dose regimen of V501 induces noninferior immune responses in girls aged 9 to 19 years who are seronegative at Day 1 to the relevant HPV type compared to young women aged 20 to 26 years who are seronegative at Day 1 to the relevant HPV type, as measured by the percentage of participants who seroconvert to each of HPV types 6, 11, 16, and 18 by 1 month post Dose 3. Each vaccine component will be analysed separately. The statistical criterion for noninferiority requires that the lower bound of two-sided 95% confidence interval for the difference (girls minus young women) in seroconversion percentages be greater than -5 percentage points for each HPV type.

  Endpoint: cLIA seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3.

- To summarize immune responses (including GMTs and seroconversion percentages) to HPV types 6, 11, 16, and 18 assessed using HPV total IgG Luminex immunoassay (IgG LIA).

  Endpoint: IgG LIA GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3.

- Objective: To evaluate the safety and tolerability of V501 in girls aged 9-19 years and young women aged 20-26 years.

  Endpoints:

  - Proportion of participants experiencing solicited injection-site adverse events (AEs),

- Proportion of participants experiencing solicited systemic Aes,
- Proportion of participants experiencing serious adverse events (SAEs)

Exploratory objective:

- To summarize immune responses (including GMTs and seroconversion percentages) to HPV types 6, 11, 16, and 18 assessed using pseudovirion-based neutralization assay (PBNA).

  Endpoint: PBNA GMTs and seroconversion percentages to each of HPV 6, 11, 16, and 18 at 1 month post dose 3.

Sample size

Approximately 766 participants were planned to be enrolled. As of the data cut-off date for this report, 766 participants were enrolled and received at least one dose of study vaccination.

Statistical Methods

To test the primary and secondary hypotheses, the immune responses among participants aged 9 to 19 years were compared with participants aged 20 to 26 years. The per-protocol immunogenicity (PPI) population was the primary population for the analysis of immune responses to each of the 4 vaccine HPV types (6, 11, 16, and 18). To be included in this population, participants must:

1) Have received all 3 study vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within the vaccination visit window specified in protocol.
2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, a participant must be seronegative for both HPV types 6 and 11.
3) Have provided Month 7 serum sample within the visit window specified in protocol.
4) At any time from Day 1 through Month 7, not meet any exclusion criteria that are deemed to potentially interfere with the evaluation of immune response to injections of qHPV vaccine.

The primary hypotheses of non-inferiority of GMTs for each of HPV types 6, 11, 16, and 18 were to be addressed by 4 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). The tests were conducted using an ANOVA model with a response of log individual titers and a fixed effect for comparison group. The statistical criterion for non-inferiority required that the lower bound of two-sided 95% confidence interval of GMT ratio (9 to 19 years old/20 to 26 years old) being greater than 0.67 for each HPV type.

The secondary hypothesis of non-inferiority of seroconversion percentages for each of the vaccine HPV types (6, 11, 16, and 18) was to be addressed by 4 one-sided tests of noninferiority (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). The tests were conducted using the method of Miettinen and Nurminen. The statistical criterion for non-inferiority required that the lower bound of two-sided 95% confidence interval for the difference (9 to 19 years old minus 20 to 26 years old) in seroconversion percentages being greater than -5 percentage points for each HPV type.

All safety data were summarized as summary statistics, counts and percentages for the two age groups. Safety analyses were based on the all participants as treated (APaT) population, which included all enrolled participants who received at least one dose of study vaccination and had clinical follow-up for safety.

Results

Participant flow

A total of 766 participants were enrolled. Five (0.7%) participants (2 from the 9 to 19 years old group vs. 3 from the 20 to 26 years old group) did not complete 3 doses of study vaccination by the visit cut-off date due to pregnancy. Eleven (1.4%) participants (5 from the 9 to 19 years old group vs. 6 from the 20 to 26 years old group) discontinued from the study vaccination with the reason of withdrawal by parent/guardian or participants. No participant discontinued study vaccination due to adverse events. Eight (1.0%) participants (3 from the 9 to 19 years old group vs. 5 from the 20 to 26 years old group) did not complete the Base Stage by the visit cut-off date mainly due to pregnancy. Three (0.4%) participants (all from the 20 to 26 years old group) discontinued early from the study with the reason of withdrawal by participant.

The number of participants who discontinued the study vaccination or withdrew from the study were generally similar across the two age groups.

Recruitment

A total of 841 healthy females between the ages of 9 and 26 were screened for eligibility in this study, 766 participants were enrolled and received at least one dose of study vaccination. A total of 75 participants who were screened for the study were not enrolled. The most common reason that prevented participants from being enrolled was that female participant of childbearing potential didn't use effective contraceptive during sexual intercourse since the first day of the last menstrual period through Day 1.

Baseline data

Overall Median Age (range):
- 9 to 19 years old group: 14.0 years (9 to 19 years)
- 20 to 26 years old group: 23.0 years (20 to 26 years)

Gender: 766 (100%) female
Race: 766 (100%) Asian (Chinese)

Participants were seronegative at Day 1 for the HPV type being analysed.

Number analysed

A total of 755 (98.6%) participants completed the Base Stage. Eight (1.0%) participants (3 from the 9 to 19 years old group vs. 5 from the 20 to 26 years old group) did not complete the Base Stage by the visit cut-off date mainly due to pregnancy. Three (0.4%) participants (all from the 20 to 26 years old group) discontinued early from the study with the reason of withdrawal by participant.

	9 to 19 Years of Age		**20 to 26 Years of Age**		**Total**	
	n	(%)	n	(%)	n	(%)
Not enrolled	29		46		75	
Subjects in population	383		383		766	
Vaccinated at						
Vaccination 1	383	(100.0)	383	(100.0)	766	(100.0)
Vaccination 2	379	(99.0)	378	(98.7)	757	(98.8)
Vaccination 3	376	(98.2)	374	(97.7)	750	(97.9)

Status for Study Medication in Trial						
Started	383		383		766	
Completed	376	(98.2)	374	(97.7)	750	(97.9)
Discontinued	5	(1.3)	6	(1.6)	11	(1.4)
Withdrawal By Parent/Guardian	3	(0.8)	0	(0.0)	3	(0.4)
Withdrawal By Subject	2	(0.5)	6	(1.6)	8	(1.0)
Ongoing*	2	(0.5)	3	(0.8)	5	(0.7)
Status for Trial Segment (Base Stage)						
Entered	383		383		766	
Completed	380	(99.2)	375	(97.9)	755	(98.6)
Discontinued	0	(0.0)	3	(0.8)	3	(0.4)
Withdrawal By Subject	0	(0.0)	3	(0.8)	3	(0.4)
Ongoing**	3	(0.8)	5	(1.3)	8	(1.0)
Status for Next Trial Segment (Extension Stage)						
Continuing Into Next Trial Segment	353	(92.2)	NA	NA	353	(46.1)
Not Continuing Into Next Trial Segment	13	(3.4)	NA	NA	13	(1.7)
Status Not Recorded	17	(4.4)	NA	NA	17	(2.2)

'Withdrawal By Subject' is equal to 'Withdrawal By Parent/Guardian' for subjects aged 9-17 years

*Subjects continued the study but has not yet completed 3-dose regimen of study vaccine due to pregnancy by the visit cutoff date for primary analyses.

**Subjects has not completed Month 7 visit mainly due to pregnancy by the visit cutoff date.

Efficacy results

Primary immunogenicity objective:

- In the PPI population, anti-HPV 6, 11, 16, and 18 cLIA GMTs at 1 month post dose 3 (Month 7) in females 9 to 19 years of age were non-inferior to those observed in females 20 to 26 years of age. The cLIA GMT ratios (9 to 19 years old group vs. 20 to 26 years old group) ranged from 1.39 to 1.66 depending on the HPV type, with the lower bound of 95% CI exceeding 0.67 and p-values <0.0001 for all vaccine HPV types, thus the primary immunogenicity objective was met.

Table 11-1
Statistical Analysis of Non-Inferiority of cLIA Geometric Mean Titers at Month 7
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=383)		20 to 26 Years of Age (N=383)		GMT Ratio(95% CI) 9-19yr/20-26yr	p-Value for Non-Inferiority[§]
	n	GMT (mMU/mL)	n	GMT (mMU/mL)		
Anti-HPV 6	343	975.2	315	686.6	1.42 (1.28,1.58)	<.0001
Anti-HPV 11	343	807.4	315	580.2	1.39 (1.25,1.55)	<.0001
Anti-HPV 16	354	4573.7	330	2989.2	1.53 (1.37,1.70)	<.0001
Anti-HPV 18	333	1176.5	318	708.6	1.66 (1.45,1.90)	<.0001

[§]For the null hypothesis that GMT (9-19 yr)/GMT(20-26 yr) ≤ 0.67, a p-value <0.025 supports a conclusion that the type-specific anti-HPV response in girls aged 9-19 years is non-inferior to that in young women aged 20-26 years at Month 7.

The estimated GMTs and associated CIs are calculated using an ANOVA model.

N = Number of participants in the indicated age group who have received at least one dose of the qHPV vaccine.

n = Number of participants contributing to the analysis.

ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV = Quadrivalent HPV.

Source: [P213V501: adam-adsl; adimm]

Secondary immunogenicity objectives:

- In the PPI population, anti-HPV 6, 11, 16, and 18 cLIA seroconversion percentages at 1 month post dose 3 (Month 7) in females 9 to 19 years of age were non-inferior to those observed in females 20 to 26 years of age. All participants seroconverted to vaccine HPV types at Month 7, with the lower bound of 95% CI for the differences in seroconversion (9 to 19 years old group minus 20 to 26 years old group) exceeding -5% and p-values <0.0001 for all vaccine HPV types, thus the secondary immunogenicity objective was met.
- In the PPI population, robust GMTs to HPV types 6, 11, 16, and 18 at 1 month post dose 3 (Month 7) were observed as measured by IgG LIA and anti-HPV IgG LIA seroconversion were 100% for all vaccine HPV types in the two age groups, which are consistent with those assessed by cLIA.

Assessor's Comment: The younger age group responded to the Gardasil with slightly higher antibody titer than the older group. This is expected result and observed earlier. The non-inferiority criteria was met and the result is very similar to the observations already described in EU SmPC. Therefore, no SmPC update is requested.

Safety results

The overall proportions of participants with AEs from Days 1 to 31 following any vaccination visit were generally comparable between the two age groups [Table 12-1]. 61.6% and 68.9% of participants reported at least one AE, 36.6% and 40.7% of participants reported at least one injection-site AE, 49.3% and 54.8% of participants reported at least one systemic AE in the 9 to 19 years old and 20 to 26 years old groups, respectively. All injection-site AEs were considered by the investigator to be vaccine-related. Approximately 30% of participants reported vaccine-related systemic AEs. Similar trends were observed for AEs reported from Day 1 to Month 7[Table 12-2].

A total of 16 participants (2.1%) experienced SAEs during the entire Base Stage period, with 6 (0.8%) reported during Days 1 to 31 following any vaccination visit. None of these SAEs were considered by the investigator to be vaccine-related. No participant discontinued the study vaccination due to AEs. No participant died during the Base Stage.

Table 12-1
Adverse Event Summary
(Days 1 to 31 Following Any Vaccination Visit) (All Participants as Treated Population)

	9 to 19 Years of Age		20 to 26 Years of Age		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	383		383		766	
with one or more adverse events	236	(61.6)	264	(68.9)	500	(65.3)
injection-site	140	(36.6)	156	(40.7)	296	(38.6)
non-injection-site	189	(49.3)	210	(54.8)	399	(52.1)
with no adverse event	147	(38.4)	119	(31.1)	266	(34.7)
with vaccine-related[†] adverse events	195	(50.9)	207	(54.0)	402	(52.5)
injection-site	140	(36.6)	156	(40.7)	296	(38.6)
non-injection-site	119	(31.1)	104	(27.2)	223	(29.1)
with non-serious adverse events	236	(61.6)	263	(68.7)	499	(65.1)
with serious adverse events	2	(0.5)	4	(1.0)	6	(0.8)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

Table 12-2
Adverse Event Summary
(Day 1 to Month 7) (All Participants as Treated Population)

	9 to 19 Years of Age		20 to 26 Years of Age		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	383		383		766	
with one or more adverse events	237	(61.9)	268	(70.0)	505	(65.9)
injection-site	140	(36.6)	156	(40.7)	296	(38.6)
non-injection-site	191	(49.9)	214	(55.9)	405	(52.9)
with no adverse event	146	(38.1)	115	(30.0)	261	(34.1)
with vaccine-related[†] adverse events	195	(50.9)	207	(54.0)	402	(52.5)
injection-site	140	(36.6)	156	(40.7)	296	(38.6)
non-injection-site	119	(31.1)	104	(27.2)	223	(29.1)
with non-serious adverse events	237	(61.9)	263	(68.7)	500	(65.3)
with serious adverse events	6	(1.6)	10	(2.6)	16	(2.1)
with serious vaccine-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the vaccine.

Source: [P213V501: adam-adsl; adae]

Assessor's Comment:

Since this is a p46 procedure that is not part of the EU RMP, only the pediatric data are assessed. The recorded AEs are well known and are previously described for Gardasil.

The observed amount of AEs are in agreement of what is already described in EU SmPC. There was no big difference of amount of AEs between two age groups.

P213X01V501

A Phase 3 Open-Label Clinical Trial to Study the Immunogenicity, Safety and Tolerability of Recombinant Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine (V501) in Chinese Girls Aged 9-19 Years and Young Women Aged 20-26 Years

Description

Extension Stage (post Month 7 through Month 60).

Methods

Study participants

365 Chinese girls aged 9 to 19 years.

Treatments

No vaccinations were administered during the Extension Stage.

Objective(s)

Primary Objective, Extension Stage:

- To evaluate persistence of immune responses induced by V501 in girls 9 to 19 years of age.

  Endpoints:

  - cLIA GMTs and seropositivity percentages to each of HPV 6, 11, 16 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60

- IgG LIA GMTs and seropositivity percentages to each of HPV 6, 11, 16 and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60

Secondary objective:

- To evaluate the safety of V501 in girls 9 to 19 years of age.

  Endpoint: Proportion of participants experiencing SAEs.

Exploratory objective:

- To summarize persistence of immune responses to HPV types 6, 11, 16, and 18 assessed using PBNA in girls 9 to 19 years of age.

  Endpoint: PBNA GMTs and seropositivity percentages to each of HPV 6, 11, 16 and 18 at month 12, Month 24, Month 36, Month 48, and Month 60.

Sample size

365 participants from the 9 to 19 years old group entered the Extension Stage.

Statistical Methods

Immunogenicity analyses were conducted in the PPI population for 9-19 years old participants who entered the Extension Stage. To be included in this PPI population, participants must:

1) Have received all 3 study vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within the pre-specified vaccination visit window.
2) Be seronegative at Day 1 for the HPV type being analyzed. In the analysis of HPV types 6 and 11, a participant must be seronegative for both HPV types 6 and 11.
3) Have provided Month 7 serum sample within the pre-specified visit window.
4) At any time from Day 1 through Month 7, not meet any exclusion criteria that were deemed to potentially interfere with the evaluation of immune response to injections of qHPV vaccine.

Anti-HPV GMTs and seropositivity percentages to HPV 6, 11, 16, and 18 at Month 12, Month 24, Month 36, Month 48, and Month 60 measured by cLIA and IgG LIA were summarized to describe the persistence of serum antibody responses to the 4 vaccine HPV types. The PBNA GMTs and seropositivity percentages to the 4 vaccine HPV types at Month 12, Month 24, Month 36, Month 48, and Month 60 were also summarized descriptively as exploratory endpoints.

Safety analyses were based on the APaT population, which included all enrolled participants who received at least one dose of study vaccination and had clinical follow-up for safety. Summary statistics, including the count and proportion of participants with SAEs during the Extension Stage were summarized for 9 to 19 years old participants.

Results

Participant flow

A total of 365 participants in the 9 to 19 years old group entered the Extension Stage; 338 (92.6%) participants completed the study, and 27 (7.4%) participants discontinued from the study during the Extension Stage.

Recruitment

Participants in the 9 to 19 years old group who received 3 doses of qHPV in the Base Stage and provided informed consent/assent for study extension were eligible to participate in the Extension Stage. Participants enrolled in the 9 to 19 years old group who reported overdose or received non-study HPV vaccines during the Base Stage were to be excluded from the Extension Stage.

Baseline data

Overall Median Age (Range): 14.0 years (9 to 19 years) (at enrolment of Base Stage)
• Gender: 365 (100%) female
• Race: 365 (100%) Asian (Chinese

Number analysed

A total of 762 (99.5%) participants completed the Base Stage (383 from the 9 to 19 years old group and 379 from the 20 to 26 years old group), and 365 participants from the 9 to 19 years old group entered the Extension Stage.

Efficacy results

- Administration of a 3-dose regimen of qHPV vaccine to Chinese females 9 to 19 years of age induces anti-HPV 6, 11, 16, and 18 antibody responses that generally persist through 5 years postvaccination 1, see Table 14.2-1.
- Anti-HPV cLIA GMTs to HPV 6, 11, 16, and 18 peaked at Month 7, decreased sharply through Month 12, and gradually thereafter through Month 60. The cLIA seropositivity percentages were 100% at Month 7 for the 4 vaccine HPV types and ranged from 58.3% to 87.1% at Month 60 depending on the HPV type.
- Consistent with the results of cLIA, anti-HPV IgG LIA GMTs to HPV 6, 11, 16, and 18 peaked at Month 7, decreased sharply through Month 12, and gradually thereafter through Month 60. The IgG LIA seropositivity percentages were 100% at Month 7 for the 4 vaccine HPV types and remained >95% at Month 60 for all 4 vaccine HPV types.

Table 14.2-1
Summary of cLIA Immune Responses by Visit
(Per-Protocol Immunogenicity Population Entered into Extension Stage)

Assay (cLIA) Study Timepoint	9 to 19 Years of Age (N=365)			
	n	GMT(mMU/mL) (95% CI)	m	Seropositivity Percentages (%) (95% CI)
Anti-HPV 6				
Day 1	332	26.1 (25.3, 26.8)	0	0.0 (0.0, 1.1)
Month 07	332	971.2 (896.9, 1051.6)	332	100.0 (98.9, 100.0)
Month 12	328	259.1 (237.6, 282.4)	325	99.1 (97.4, 99.8)
Month 24	322	137.9 (125.5, 151.4)	286	88.8 (84.9, 92.0)
Month 36	318	110.6 (101.3, 120.7)	266	83.6 (79.1, 87.5)
Month 48	311	103.0 (94.4, 112.4)	213	68.5 (63.0, 73.6)
Month 60	307	87.6 (80.4, 95.4)	190	61.9 (56.2, 67.3)
Anti-HPV 11				
Day 1	332	16.3 (16.2, 16.4)	0	0.0 (0.0, 1.1)
Month 07	332	805.2 (745.3, 869.9)	332	100.0 (98.9, 100.0)
Month 12	328	206.7 (190.5, 224.3)	327	99.7 (98.3, 100.0)
Month 24	322	110.3 (101.0, 120.6)	307	95.3 (92.4, 97.4)
Month 36	318	87.0 (79.6, 95.2)	293	92.1 (88.6, 94.8)
Month 48	311	81.8 (74.8, 89.3)	265	85.2 (80.8, 89.0)
Month 60	307	67.3 (61.6, 73.5)	230	74.9 (69.7, 79.7)
Anti-HPV 16				
Day 1	342	20.2 (20.0, 20.3)	0	0.0 (0.0, 1.1)
Month 07	342	4507.0 (4167.3, 4874.4)	342	100.0 (98.9, 100.0)
Month 12	338	1149.8 (1054.6, 1253.7)	338	100.0 (98.9, 100.0)
Month 24	333	522.6 (472.1, 578.5)	332	99.7 (98.3, 100.0)
Month 36	329	400.8 (359.5, 446.8)	325	98.8 (96.9, 99.7)
Month 48	321	347.5 (310.0, 389.6)	295	91.9 (88.4, 94.6)
Month 60	317	283.2 (250.8, 319.8)	276	87.1 (82.9, 90.6)
Anti-HPV 18				
Day 1	323	37.0 (36.1, 38.1)	0	0.0 (0.0, 1.1)
Month 07	323	1171.8 (1059.9, 1295.4)	323	100.0 (98.9, 100.0)
Month 12	320	284.2 (257.3, 313.8)	310	96.9 (94.3, 98.5)
Month 24	316	157.2 (142.7, 173.3)	277	87.7 (83.5, 91.1)
Month 36	312	131.9 (120.2, 144.8)	262	84.0 (79.4, 87.9)
Month 48	305	130.3 (118.9, 142.7)	197	64.6 (58.9, 70.0)
Month 60	302	113.6 (103.7, 124.5)	176	58.3 (52.5, 63.9)

The estimated GMTs and associated CIs are calculated using t-distribution.
The estimated seropositivity percentages and associated CIs are calculated using the exact binomial method of Clopper and Pearson.
The seropositivity percentages represents proportion of participants with anti-HPV serum levels ≥ 50, 29, 41, and 59 mMU/mL for timepoints before and at Month 36 and ≥ 65, 37, 79, and 85 mMU/mL for Month 48 and afterfor HPV types 6, 11, 16, and 18, respectively.
N = Number of participants in the indicated age group who have received 3 doses of the qHPV vaccine and entered the extension stage.
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; qHPV = Quadrivalent HPV.

Source: [P213X01V501: adam-adsl; adimm]

Assessor´s comment: the antibody kinetics over time followed a pattern which is common for all vaccines. The highest antibody level was observed after the final vaccine dose and thereafter the antibody level started to decline, but still being detectable over years and still being much higher than before vaccination. The antibody kinetics over time has been described for Gardasil earlier and the current observation confirms the earlier results.

Safety results

- A total of 12 SAEs were reported by 8 participants (2.2%) during the entire Extension Stage. None of the SAEs were considered to be vaccine related by the investigator.
- No participant died during the Extension Stage
- Administration of a 3-dose regimen of qHPV vaccine to Chinese females 9 to 19 years of age is generally well tolerated through 5 years postvaccination 1.

2.3.3. Discussion on clinical aspects

The results are in agreement with previously reported studies and no concerns regarding lacking efficacy or new safety issues are raised from this study.

3. Rapporteur's overall conclusion and recommendation

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

☒ Fulfilled:

No regulatory action required.