Amsterdam, 30 January 2025
EMA/CHMP/56408/2025
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, as amended

Gardasil 9

human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

Procedure no.: EMEA/H/C/003852/P46/014

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	2024-12-02	2024-12-02
☐	CHMP Rapporteur Assessment Report	2025-01-06	2024-12-23
☐	CHMP members comments	2025-01-20	2025-01-20
☐	Updated CHMP Rapporteur Assessment Report	2025-01-23	N/A
☒	CHMP adoption of conclusions:	2025-01-30	2025-01-30

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1. Introduction

On November 18, 2024, the MAH submitted a completed paediatric study for Gardasil 9 (9vHPV), 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 study V503-066, A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

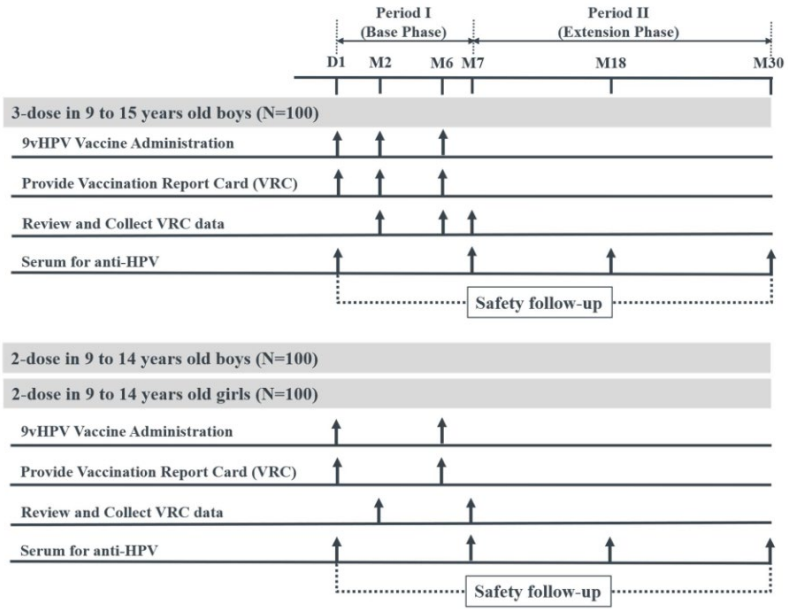
- V503-066, A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 Years of Age

2.3.2. Clinical study

V503-066, A Phase 3, Open-label Clinical Study to Evaluate the Immunogenicity and Safety of 9vHPV Vaccine, in Japanese Boys and Girls, 9 to 15 Years of Age

Description

Study design



Methods

Study participants

Eligible participants were healthy Japanese boys aged 9 to 15 years or girls aged 9 to 14 years who had not yet had coitarche and had not previously received an HPV vaccine.

Treatments

HPV Type 6/11/16/18/31/33/45/52/58 vaccine contains L1 VLP 30/40/60/40/20/20/20/20/20 µg respectively in 0.5 mL per dose. A total of 3 vaccinations were given on Day 1, Month 2 and Month 6 or 2 vaccinations on Day 1 and Month 6.

Objectives/ endpoints

Primary immunogenicity objectives: To estimate percent seroconversion for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 in Japanese aged 9 to 15 years who received the 9vHPV vaccine.

- Boys after 3 doses
- Boys after 2 doses
- Girls after 2 doses

Endpoints: Serum antibody titer to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 measured using cLIA binding assay

Safety primary objective: To evaluate the safety and tolerability of the 9vHPV vaccine in Japanese boys aged 9 to 15 years who received 3 doses and Japanese boys and girls aged 9 to 14 years who received 2 doses of the 9vHPV vaccine.

Endpoints: -Solicited injection-site adverse events

- Systemic adverse events

- Serious adverse events

Secondary immunogenicity objectives: To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at Month 7 including geometric mean titers (GMTs) in Japanese aged 9 to 15 years who received the 9vHPV vaccine for the same subgroups named above.

Exploratory objective: to assess the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antibody responses at Month 18 and 30.

Sample size

The planned enrolment total was 300 participants (100 in the 3-dose boy arm, 100 in the 2- dose boy arm, 100 in the 2-dose girl arm). A total of 314 participants were allocated/randomized (105 allocated/randomized to the 3-dose boy arm, 104 allocated/randomized to the 2-dose boy arm, 105 allocated to the 2-dose girl arm).

Randomisation and blinding (masking)

The study was open labelled. IRT system was used to allocate participants to either the 3-dose or 2-dose regimen arms based on gender and age at the time of providing the informed consent.

Fifteen-years-old boys were assigned to the 3-dose regimen arm until the boys 3-dose regimen arms reaches 100 participants. Girls aged 9 to 14 years were assigned to the 2- dose regimen arm without randomization until the girls 2-dose regimen arm reaches 100 participants.

Statistical Methods

The primary population for the analysis of immune response was per protocol population (PPI), which consisted of participants who received study vaccine with the correct dose within acceptable day ranges, had provided blood samples for serology testing within 21 to 49 days post last dose, was seronegative to the appropriate HPV type(s) at Day 1, and had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine.

The primary immunogenicity endpoints were seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses and 2 doses of the 9vHPV vaccine. Seroconversion to a specific HPV type was defined as changing serostatus from seronegative at Day 1 to seropositive at 1 month post last dose (Month 7). Percent seroconversion was evaluated by computing point estimates and constructing 95% CI of the percentage of participants who seroconvert at 1 month post last dose (Month 7). Calculation of the 95% CI of percent seroconversion was based on the exact binomial method proposed by Clopper and Pearson.

The key secondary endpoints were cLIA GMTs for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 at 1 month post last dose (Month 7) following 3 doses and 2 doses of the 9vHPV vaccine. GMTs and corresponding 95% CIs were derived by taking the anti-logarithm of the mean and corresponding 95% CI of the mean of the log-transformed anti-HPV titers.

The key safety endpoint was to summarize for each study arm the incidence of solicited injection-site Adverse Events (AEs) (redness/erythema, swelling, and tenderness/pain) occurring Days 1 to 5 following any vaccination, systemic AEs occurring Days 1 to 15 following any vaccination, SAEs, and serious vaccine-related AEs occurring any time during the study.

Safety analysis was conducted in the all participants as treated (APaT) population, which consisted of all participants who received at least 1 dose of 9vHPV vaccine and have provided safety data at any time during the study. Participants were included in the study arm corresponding to the study vaccination regimen they actually received for the analysis of safety data using the APaT population.

Results

Participant flow

A total of 105 participants (9- to 14-year-old girls) were randomized to receive 2 doses of 9vHPV vaccine at Day 1 and Month 6; 104 participants received at least 1 dose of 9vHPV vaccine, completed 2 doses of 9vHPV vaccine, and completed the study. One participant was allocated/randomized but did not receive the study intervention due to withdrawal by participant prior to vaccination [Table 1].

A total of 104 participants (9- to 14-year-old boys) were randomized to receive 2 doses of 9vHPV vaccine at Day 1 and Month 6; all 104 participants received at least 1 dose of 9vHPV vaccine, received 2 doses of 9vHPV vaccine, and completed the study [Table 1].

A total of 105 participants (9- to 15-year-old boys) were randomized to receive 3 doses of 9vHPV vaccine at Day 1, Month 2, and Month 6; 104 participants received at least 1 dose of 9vHPV vaccine,

103 participants received 3 doses of 9vHPV vaccinations, and 101 participants completed the study. One participant was allocated/randomized but did not receive the study intervention due to physician decision prior to vaccination. One participant received only 2 doses of the study vaccine (at Day 1 and Month 2) and did not complete all doses of protocol-specified study intervention. Two participants discontinued during the Extension Phase after completion of the specified number of vaccinations. The reasons of study discontinuation after vaccination were all withdrawal by participants.

Table 1. Disposition of Participants

	9-15 years old boys (0, 2, 6 Regimen)		9-14 years old boys (0, 6 Regimen)		9-14 years old girls (0, 6 Regimen)	
	n	(%)	n	(%)	n	(%)
Participants in population	105		104		105	
Vaccinated at						
Treatment 1	104	(99.0)	104	(100.0)	104	(99.0)
Treatment 2	104	(99.0)	104	(100.0)	104	(99.0)
Treatment 3	103	(98.1)	0	(0.0)	0	(0.0)
Trial Disposition						
Completed	101	(96.2)	104	(100.0)	104	(99.0)
Discontinued	4	(3.8)	0	(0.0)	1	(1.0)
Physician Decision	1	(1.0)	0	(0.0)	0	(0.0)
Withdrawal By Subject	3	(2.9)	0	(0.0)	1	(1.0)
Participant Study Medication Disposition						
Completed	103	(98.1)	104	(100.0)	104	(99.0)
Discontinued	1	(1.0)	0	(0.0)	0	(0.0)
Withdrawal By Subject	1	(1.0)	0	(0.0)	0	(0.0)
Status Not Recorded	1	(1.0)	0	(0.0)	1	(1.0)
Each participant is counted once for Trial Disposition, Participant Study Medication Disposition based on the latest corresponding disposition record.						

Source: [P066V503: adam-adsl; adex]

Immunogenicity analysis population

The primary immunogenicity analyses (Table 2.) of the Base Phase and Extension Phase were conducted in the PPI population consisting of individuals who:

-Received all required vaccinations of 9vHPV vaccine with the correct dose within acceptable day ranges

-Provided blood samples for serology testing within 21 to 49 days post last dose

-Were seronegative to the appropriate HPV type(s) at Day 1

-Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine.

Table 2. Immunogenicity Analysis Population

	9-15 years old boys (0, 2, 6 Regimen) (N=105)	9-14 years old boys (0, 6 Regimen) (N=104)	9-14 years old girls (0, 6 Regimen) (N=105)
	n	n	n
Number of Participants who received at least 1 injection[a]	**104**	**104**	**104**
Included in Per-Protocol Immunogenicity Population			
HPV 6	90	91	98
HPV 11	90	91	98
HPV 16	98	98	100
HPV 18	94	92	97
HPV 31	90	93	98
HPV 33	85	90	98
HPV 45	94	95	100
HPV 52	97	96	102
HPV 58	101	100	103
Excluded from Per-Protocol Immunogenicity Population			
HPV 6	14	13	6
HPV 11	14	13	6
HPV 16	6	6	4
HPV 18	10	12	7
HPV 31	14	11	6
HPV 33	19	14	6
HPV 45	10	9	4
HPV 52	7	8	2
HPV 58	3	4	1
Reason for Exclusion[b]			
General protocol violation	0	0	1
Missed 1st, 2nd or 3rd vaccination	1	1	0
Serology samples collected out of acceptable day range or missing Month 7 serology samples/results[cd]	1	1	0
Reason for Exclusion[b]			
Positive to HPV 6 or 11 at Day 1[e]	12	12	6
Positive to HPV 16 at Day 1[e]	5	4	3
Positive to HPV 18 at Day 1[e]	9	10	7
Positive to HPV 31 at Day 1[e]	13	9	5
Positive to HPV 33 at Day 1[e]	18	12	5
Positive to HPV 45 at Day 1[e]	8	7	4
Positive to HPV 52 at Day 1[e]	6	6	1
Positive to HPV 58 at Day 1[e]	2	2	0

[a]Participants who did not receive at least 1 injection were excluded from all analysis populations.

[b]Participants are counted once in each applicable exclusion category. A participant may appear in more than one category.

[c]Among participants who received all 2 or 3 vaccinations.

[d]Includes participants with a missing serum sample or missing cLIA results for ≥ 1 HPV-type.

[e]Seropositive at Day 1. Applies only to the analysis populations for the respective HPV-type(s).

N = Number of participants enrolled; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus;

Source: [P066V503: adam-adsl]

Recruitment

Baseline data

All of the participants in all study arms were Japanese. The median age of participants was 12.0 years (range: 9 to 15 years) for the 3-dose boy arm and 11.0 years (range: 9 to 14 years) for the 2-dose boy arm and the 2-dose girl arm (Table 3).

Table 3. Participants Characteristics

	9-15 years old boys (0, 2, 6 Regimen)		9-14 years old boys (0, 6 Regimen)	
	n	(%)	n	(%)
Participants in population	105		104	
Sex				
Male	105	(100.0)	104	(100.0)
Age (Years)				
8	0	(0.0)	0	(0.0)
9 to 10	34	(32.4)	36	(34.6)
11 to 12	30	(28.6)	29	(27.9)
13 to 14	29	(27.6)	39	(37.5)
15	12	(11.4)	0	(0.0)
Mean	11.8		11.5	
SD	2.0		1.7	
Median	12.0		11.0	
Range	9 to 15		9 to 14	
Weight (kg)				
Participants with data	104		104	
Mean	44.6		40.7	
SD	13.5		11.0	
Median	42.9		39.8	
Range	24.2 to 79.4		20.9 to 72.0	
BMI (kg/m^2)				
Participants with data	104		104	
Mean	19.0		18.0	
SD	3.5		2.7	
Median	18.3		17.4	
Range	14.2 to 29.7		14.0 to 30.8	

Table 4. Baseline serology at Day 1

Day 1 Composite HPV 6/11/16/18/31/33/45/52/58 Status	9-15 years old boys (0, 2, 6 Regimen) (N=105)		9-14 years old boys (0, 6 Regimen) (N=104)		9-14 years old girls (0, 6 Regimen) (N=105)	
	m/n	(%)	m/n	(%)	m/n	(%)
Negative to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 By serology	74/104	(71.2)	77/104	(74.0)	89/104	(85.6)
Positive to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58 By serology	30/104	(28.8)	27/104	(26.0)	15/104	(14.4)

Percentages are calculated as 100*(m/n).
Positive (Negative) 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-types 6, 11, 16, 18, 31, 33, 45, 52 and 58, respectively.
N = Number of participants enrolled.
m = Number of participants in the respective category.
n = Number of participants with non-missing data (serology) at Day 1 for HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58.
cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus;

Source: [P066V503: adam-adsl]

Number analysed

Efficacy results

Primary Immunogenicity Endpoint: Seroconversion at 1 month post last dose (Month 7)

All (100%) of participants in the PPI population of the 3-dose boy arm and the 2-dose boy arm and girls arm had seroconverted for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 1 month post last dose (Month 7) [Table 5 and 6].

Table 5. Seropositivity rates for boys

Assay (cLIA)	Time Point	9-15 years old boys (0, 2, 6 Regimen) (N=104)				9-14 years old boys (0, 6 Regimen) (N=104)			
		n	m	Seropositive Percent	(95% CI)	n	m	Seropositive Percent	(95% CI)
Anti-HPV 6	Day 1	90	0	0.0	(0.0, 4.0)	91	0	0.0	(0.0, 4.0)
	Month 7	90	90	100.0	(96.0, 100.0)	91	91	100.0	(96.0, 100.0)
	Month 18	89	86	96.6	(90.5, 99.3)	90	88	97.8	(92.2, 99.7)
	Month 30	88	83	94.3	(87.2, 98.1)	91	88	96.7	(90.7, 99.3)
Anti-HPV 11	Day 1	90	0	0.0	(0.0, 4.0)	91	0	0.0	(0.0, 4.0)
	Month 7	90	90	100.0	(96.0, 100.0)	91	91	100.0	(96.0, 100.0)
	Month 18	89	89	100.0	(95.9, 100.0)	90	89	98.9	(94.0, 100.0)
	Month 30	88	87	98.9	(93.8, 100.0)	91	87	95.6	(89.1, 98.8)
Anti-HPV 16	Day 1	98	0	0.0	(0.0, 3.7)	98	0	0.0	(0.0, 3.7)
	Month 7	98	98	100.0	(96.3, 100.0)	98	98	100.0	(96.3, 100.0)
	Month 18	97	97	100.0	(96.3, 100.0)	97	97	100.0	(96.3, 100.0)
Anti-HPV 18	Day 1	94	0	0.0	(0.0, 3.8)	92	0	0.0	(0.0, 3.9)
	Month 7	94	94	100.0	(96.2, 100.0)	92	92	100.0	(96.1, 100.0)
	Month 18	93	90	96.8	(90.9, 99.3)	91	83	91.2	(83.4, 96.1)
	Month 30	92	82	89.1	(80.9, 94.7)	92	83	90.2	(82.2, 95.4)
Anti-HPV 31	Day 1	90	0	0.0	(0.0, 4.0)	93	0	0.0	(0.0, 3.9)

Assay (cLIA)	Time Point	9-15 years old boys (0, 2, 6 Regimen) (N=104)				9-14 years old boys (0, 6 Regimen) (N=104)			
				Seropositive				Seropositive	
		n	m	Percent	(95% CI)	n	m	Percent	(95% CI)
Anti-HPV 31	Month 7	90	90	100.0	(96.0, 100.0)	93	93	100.0	(96.1, 100.0)
	Month 18	89	88	98.9	(93.9, 100.0)	92	89	96.7	(90.8, 99.3)
	Month 30	89	83	93.3	(85.9, 97.5)	93	90	96.8	(90.9, 99.3)
Anti-HPV 33	Day 1	85	0	0.0	(0.0, 4.2)	90	0	0.0	(0.0, 4.0)
	Month 7	85	85	100.0	(95.8, 100.0)	90	90	100.0	(96.0, 100.0)
	Month 18	84	84	100.0	(95.7, 100.0)	89	88	98.9	(93.9, 100.0)
	Month 30	83	82	98.8	(93.5, 100.0)	90	88	97.8	(92.2, 99.7)
Anti-HPV 45	Day 1	94	0	0.0	(0.0, 3.8)	95	0	0.0	(0.0, 3.8)
	Month 7	94	94	100.0	(96.2, 100.0)	95	95	100.0	(96.2, 100.0)
	Month 18	93	91	97.8	(92.4, 99.7)	94	83	88.3	(80.0, 94.0)
	Month 30	92	86	93.5	(86.3, 97.6)	95	78	82.1	(72.9, 89.2)
Anti-HPV 52	Day 1	97	0	0.0	(0.0, 3.7)	96	0	0.0	(0.0, 3.8)
	Month 7	97	97	100.0	(96.3, 100.0)	96	96	100.0	(96.2, 100.0)
	Month 18	96	92	95.8	(89.7, 98.9)	95	92	96.8	(91.0, 99.3)
	Month 30	95	86	90.5	(82.8, 95.6)	96	90	93.8	(86.9, 97.7)
Anti-HPV 58	Day 1	101	0	0.0	(0.0, 3.6)	100	0	0.0	(0.0, 3.6)
	Month 7	101	101	100.0	(96.4, 100.0)	100	100	100.0	(96.4, 100.0)

Anti-HPV 58	Month 18	100	99	99.0	(94.6, 100.0)	99	98	99.0	(94.5, 100.0)
	Month 30	99	97	98.0	(92.9, 99.8)	100	98	98.0	(93.0, 99.8)

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.
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 enrolled to the respective vaccination group who received at least 1 injection.
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: [P066V503: adam-adsl; adimm]

Table 6. Seropositivity rates for girls

		9-14 years old girls (0, 6 Regimen) (N=104)			
				Seropositive	
Assay (cLIA)	Time Point	n	m	Percent	(95% CI)
Anti-HPV 6	Day 1	98	0	0.0	(0.0, 3.7)
	Month 7	98	98	100.0	(96.3, 100.0)
	Month 18	98	96	98.0	(92.8, 99.8)
	Month 30	98	96	98.0	(92.8, 99.8)
Anti-HPV 11	Day 1	98	0	0.0	(0.0, 3.7)
	Month 7	98	98	100.0	(96.3, 100.0)
	Month 18	98	98	100.0	(96.3, 100.0)
	Month 30	98	98	100.0	(96.3, 100.0)
Anti-HPV 16	Day 1	101	0	0.0	(0.0, 3.6)
	Month 7	101	101	100.0	(96.4, 100.0)
	Month 18	101	101	100.0	(96.4, 100.0)
	Month 30	101	101	100.0	(96.4, 100.0)
Anti-HPV 18	Day 1	97	0	0.0	(0.0, 3.7)
	Month 7	97	97	100.0	(96.3, 100.0)
	Month 18	97	95	97.9	(92.7, 99.7)
	Month 30	97	93	95.9	(89.8, 98.9)
Anti-HPV 31	Day 1	99	0	0.0	(0.0, 3.7)
	Month 7	99	99	100.0	(96.3, 100.0)
	Month 18	99	97	98.0	(92.9, 99.8)
	Month 30	99	98	99.0	(94.5, 100.0)

Anti-HPV 33	Day 1	99	0	0.0	(0.0, 3.7)
	Month 7	99	99	100.0	(96.3, 100.0)
	Month 18	99	99	100.0	(96.3, 100.0)
	Month 30	99	99	100.0	(96.3, 100.0)
Anti-HPV 45	Day 1	100	0	0.0	(0.0, 3.6)
	Month 7	100	100	100.0	(96.4, 100.0)
	Month 18	100	96	96.0	(90.1, 98.9)
	Month 30	100	93	93.0	(86.1, 97.1)
Anti-HPV 52	Day 1	103	0	0.0	(0.0, 3.5)
Anti-HPV 52	Month 7	103	103	100.0	(96.5, 100.0)
	Month 18	103	102	99.0	(94.7, 100.0)
	Month 30	103	99	96.1	(90.4, 98.9)
Anti-HPV 58	Day 1	104	0	0.0	(0.0, 3.5)
	Month 7	104	104	100.0	(96.5, 100.0)
	Month 18	104	104	100.0	(96.5, 100.0)
	Month 30	104	103	99.0	(94.8, 100.0)

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.
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 enrolled to the respective vaccination group who received at least 1 injection.
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: [P066V503: adam-adsl: adimm]

Secondary Immunogenicity Analyses

In the PPI population, GMTs in 9- to 14-year-old girls and boys who received 2 doses and 9- to 15-year-old boys who received 3 doses increased substantially for all 9 vaccine-targeted HPV types at Month 7 following completion of the assigned 9vHPV vaccine regimen.

Tertiary/Exploratory Analyses

Administration of a 3-dose regimen of 9vHPV vaccine to boys 9- to 15-years-old and a 2-dose regimen of 9vHPV vaccine to boys and girls 9- to 14-years-old induced antibody responses to all 9 vaccine-targeted HPV types that generally persisted through Month 18 and Month 30.

Percentages of participants who were seropositive at Month 30 ranged from 93.0% to 100.0% in girls 9- to 14-years-old (2-dose regimen), 82.1% to 99.0% in boys 9- to 14-years-old (2-dose regimen), and 89.1% to 99.0% in boys 9- to 15-years-old (3-dose regimen), depending on the HPV type (Table 5).

Safety results

Safety population

Safety analysis was conducted in the APaT population, which consisted of all participants who received at least 1 dose of 9vHPV vaccine and have provided safety data at any time during the study. Participants were included in the study arm corresponding to the study vaccination regimen they received for the analysis of safety data using the APaT population (ie, 3 doses [Day 1, Month 2, Month 6 regimen] or 2 doses [Day 1, Month 6 regimen] of 9vHPV vaccine).

Overall Adverse Events

Injection-site Adverse Events

Overall, 88.5% of the 9- to 14-year-old girls who received 2 doses (2-dose girl arm), 81.7% of the 9- to 14-year-old boys who received 2 doses (2-dose boy arm), and 84.5% of the 9- to 15-year-old boys who received 3 doses (3-dose boy arm) reported at least 1 injection-site AE from Days 1 to 5 following any vaccination visit. The most frequently reported (≥5%) injection-site AEs were pain, swelling, erythema, and pruritus across all participants.

Most injection-site AEs from Day 1 to Day 5 following any vaccination visit were mild or moderate in intensity. One participant each in the 2-dose girl arm and 2-dose boy arm reported injection-site pain of severe intensity. Both events resolved by 4 days or less following vaccination.

Of the participants with solicited injection-site AEs of erythema and swelling, the majority were 0 to ≤1 inch in size.

- Injection-site erythema >1 inch to ≤3 inches in maximum size was reported for 4 participants each in the 2-dose girl arm and the 3-dose boy arm, and 1 participant in the 2-dose boy arm.

- Injection-site swelling >1 inch to ≤4 inches in maximum size was reported for 14 participants in the 2-dose girl arm, 8 participants in the 2-dose boy arm, and 15 participants in the 3-dose boy arm.

- All injection-site swelling or erythema of >2 inches to ≤4 inches in size resolved within 1 week in the 2-dose boy and girl arms and the 3-dose boy arm.

Systemic Adverse Events

Overall, 31.7% of participants in the 2-dose girl arm, 39.4% of participants in the 2-dose boy arm, and 53.4% of participants in the 3-dose boy arm reported at least 1 systemic AE from Days 1 to 15 following any vaccination visit. The most frequently reported (≥5.0%) systemic AEs were pyrexia and headache. In addition, nasopharyngitis was also reported for 5.8% of participants in the 3-dose boy arm.

Overall, 15.4% of participants in the 2-dose girl arm, 20.2% of participants in the 2-dose boy arm, and 29.1% of participants in the 3-dose boy arm reported at least 1 vaccine-related systemic AE from Days 1 to 15 following any vaccination visit. The most frequently (≥5.0%) reported vaccine-related systemic AEs were pyrexia and headache. Headache was reported for 4.8% of participants in the 2-dose boy arm.

Overall, the majority of systemic AEs from Day 1 to Day 15 following any dose of vaccine were mild or moderate in intensity. One participant in the 3-dose boy arm experienced a severe vaccine-related systemic AE (malaise) as assessed by the investigator. The event occurred on the day of Vaccination 2 (Day 50) and resolved within 5 days.

Elevated Temperatures

No participants had a maximum temperature ≥38.0°C in the 2-dose girl arm.

No participants in the 2-dose boy arm or the 3-dose boy arm had a maximum temperature ≥38.5°C.

Serious Adverse Events

No deaths and no vaccine-related SAEs were reported during the entire study.

From Day 1 through end of study, SAEs were reported for 3 participants (2.9%) in the 2-dose girl arm and for 2 participants (1.9%) in the 2-dose boy arm. All reported SAEs resolved; no SAEs were reported in the 3-dose boy arm.

Discontinuations Due to an AE

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

Summary of Safety Results

- The most common injection-site AEs were pain, swelling, erythema, and pruritus. Most injection-site AEs were mild or moderate in intensity. Most injection-site AEs of erythema and swelling were ≤1 inch in size.
- The most common systemic AEs were pyrexia and headache. Most systemic AEs were mild or moderate in intensity.
- No vaccine-related SAEs were reported. No participant died during the study. No participant discontinued the study vaccination due to AEs.

2.3.3. Discussion on clinical aspects

Administration of the 3-dose and 2 -dose regimen of the 9vHPV vaccine to 9-to 15-year-old Japanese boys and girls demonstrated 100% seroconversion percentages for all vaccine included HPV types at 1 month post last dose and induced durable immune responses for 18 and 30 months post- vaccination.

The results are in agreement with previously reported studies. No concern regarding lacking efficacy is raised from this study.

The study population was relatively small (about N=100 in each arm, altogether N=300) and therefore the chance to detect rare AEs and SAEs is low. The safety results are also in agreement with previously reported studies. No new safety concern is raised from this study.

3. Rapporteur's 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.