14 November 2019
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Gardasil 9

Human papillomavirus vaccine rDNA

Procedure no: EMEA/H/C/003852/P46/008

Note

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

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Need for plenary discussion	No

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1. Introduction

On August 20, 2019, the MAH submitted a completed paediatric study for Gardasil 9, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that V503-P017 A Phase III Open-label Safety and Immunogenicity Study of Gardasil 9 Administered to 9- to 26- Year-Old Females and Males in Vietnam is a standalone study.

Gardasil 9 (9vHPV) was licensed in the EU at 2015.

The 9vHPV vaccine was developed to provide protection against infection and disease caused by 7 cancer-causing HPV types (HPV 16, 18, 31, 33, 45, 52 and 58), which are together responsible for approximately 90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers, and 2 HPV types (HPV 6 and 11) which are responsible for 90% of genital warts worldwide.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation of Gardasil 9 (also known as 9vHPV vaccine or V503), batch number: R003279, was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

V503-P017: A Phase III Open-label Safety and Immunogenicity Study of Gardasil9 Administered to 9- to 26- Year-Old Females and Males in Vietnam.

EudraCT: 2017-001205-33
NCT: NCT03546842

2.3.2. Clinical study

V503-P017: A Phase III Open-label Safety and Immunogenicity Study of GARDASIL 9 Administered to 9- to 26- Year-Old Females and Males in Vietnam

Description

A local immunogenicity and safety study were conducted to support 9vHPV vaccine registration in Vietnam.

Methods

Objectives and endpoints

Protocol V503-017 was designed to evaluate the immunogenicity and safety of the 9-valent Human Papillomavirus (9vHPV) [Types 6, 11, 16, 18, 31, 33, 45, 52, 58] L1 Virus-Like Particle (VLP) Recombinant Vaccine (hereafter referred to as the 9vHPV vaccine) in males and females of 9 to 26 years in Vietnam.

Table 1. Objectives and endpoints of the study

Objective/Hypothesis	Endpoint
Primary	
• Objective: To demonstrate that the 9vHPV vaccine is immunogenic • Hypothesis: 9vHPV vaccine induces acceptable anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 seroconversion at 4 weeks post Dose 3. The statistical criterion for acceptable anti-HPV seroconversion requires the lower limit of the 95% confidence interval (CI) of the percent of participants who seroconverted to be greater than 90% for each HPV type.	• Seroconversion, defined as a participant who was anti-HPV seronegative at Day 1 and became seropositive at 4 weeks post Dose 3.
Secondary	
• Objective: To evaluate the safety of 9vHPV vaccine.	• Proportion of participants experiencing solicited injection-site adverse events (AEs). • Proportion of participants experiencing solicited systemic AEs. • Proportion of participants experiencing vaccine-related serious AEs (SAEs).
• Objective: To summarize geometric mean titers (GMTs) at Day 1 and at 4 weeks post Dose 3 of 9vHPV vaccine.	• GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Day1 and 4 weeks post Dose 3.

Immunogenicity Endpoints

The purpose of the HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 Competitive Luminex Immunoassay (cLIA) or HPV-9 cLIA is to measure antibodies to HPV VLP types 6, 11, 16, 18, 31, 33, 45, 52, and 58 before and after vaccination with the 9vHPV vaccine. This assay was performed by Q2 Solutions Vaccines (San Juan Capistrano, California, USA) to evaluate the serological response following vaccination.

The primary immunogenicity endpoints are the seroconversion percentages to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 by 4 weeks post Dose 3. Seroconversion is defined as changing a participant's serostatus from seronegative at Day 1 to seropositive by 4 weeks post Dose 3. A

participant with anti-HPV cLIA (competitive Luminex immunoassay) titre at or above the serostatus cut-off for a given HPV type is considered seropositive for that HPV type.

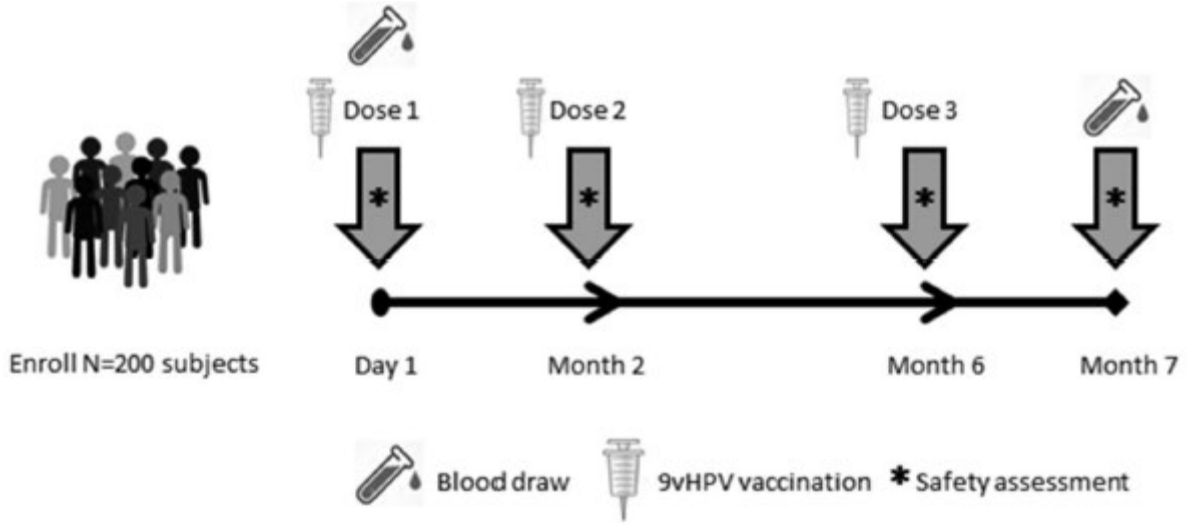
The serostatus cut-off is the antibody titre level within the assay's quantifiable range that reliably distinguishes "negative" from "positive" samples. The quantifiable range of the assay is the range of the standard curve over which test sample results had acceptable precision. To determine the serostatus cut off, a bridging study was performed to compare reportable results from the Q^2 version of the HPV-9 cLIA to historical results generated using the previous version of the assay. The serostatus cut-offs for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 50, 29, 41, 59, 29, 22, 15, 20, and 15 mMU/mL, respectively.

The secondary immunogenicity endpoints are GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post Dose 3.

Study design

Protocol V503-017 was an open-label, single-centre and single-group assignment study to evaluate the immunogenicity and safety of the 9vHPV vaccine in 9 to 26-year-old females and males in Vietnam.

Figure 1. Study design



Study population /Sample size

Approximately 200 healthy participants were planned to be enrolled. Enrolment was stratified by age and gender according to the following factors:

- Age: 1:1 allocation between 9 to 15 and 16 to 26-year-old age strata.
- Gender: 2:1 allocation between females and males within each of the 9 to 15 and 16 to 26-year-old age strata.

Additionally, enrolment limits were applied in the 9 to 15 years age group to ensure ≥30% enrolment into each of the following 2 age subgroups (with a minimum number of female and male participants in each age subgroup): 9 to 12 years and 13 to 15 years (at least 20 female and 10 male participants in each age subgroup).

Treatments

Participants were to receive a 3-dose regimen (Day 1, Month 2, and Month 6) of the 9vHPV vaccine. 9vHPV vaccine (0.5 mL) was administered as an intramuscular injection into the deltoid muscle of the non-dominant arm. Serum samples for measurement of anti-HPV antibodies were collected on Day 1 and Month 7 or approximately 4 weeks after administration of Dose 3. The safety of the vaccine was evaluated in all participants who received at least one dose of vaccine and provided safety data at any time during the study. Safety information was collected from Day 1 through Month 7.

Statistical Methods

Immunogenicity Analyses

The Per-Protocol Immunogenicity (PPI) population served as the primary population for the analysis of immune response to each of the HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in this study. The PPI population was HPV type-specific and consisted of all allocated participants who:

- Were seronegative to the appropriate HPV type at Day 1;
- Received all 3 vaccinations with the correct dose of 9vHPV vaccine within acceptable day ranges as specified in the protocol;
- Provided serum a sample within 21 to 49 days post-dose 3;
- Had no protocol deviations that could interfere with the evaluation of participant's immune response to 9vHPV vaccination. At Day 1, participants 9 to 15 years of age had to satisfy Inclusion Criterion 4 (i.e., "Had not yet had coitarche and did not plan on becoming sexually active during the vaccination period [Day 1 through Month 7]").

The primary immunogenicity hypothesis was addressed by calculating point and 95% CI estimates of percent seroconversion. The 95% CI estimate was derived based on exact binomial calculations. The statistical criterion for acceptable anti-HPV seroconversion required the lower limit of the 95% CI of the percent of participants who seroconverted to be greater than 90% for each HPV type.

The corresponding tests of hypothesis for each of these HPV types were conducted at 1-sided Type I error level of 0.025. No adjustment for multiplicity was required since success was required for all of the 9 HPV types tested.

The secondary immunogenicity objective was addressed by calculating point and 95% CI estimates of GMTs.

Safety Analyses

The All Patients as Treated (APaT) analysis population was used for safety analyses which consisted of all allocated participants who received at least one dose of 9vHPV vaccine and had provided safety data at any time during the study.

Since this was a single-group study with no comparator group, safety assessments were descriptive in nature.

Results

Recruitment/ Number analysed

A total of 205 participants were screened for the study; 4 were ineligible due to certain inclusion/exclusion criteria. The remaining 201 participants were randomized at a single-centre. One of

the randomized participants did not receive 9vHPV vaccine and was therefore excluded from all immunogenicity and safety analyses.

Almost all participants (98.5%) completed the 3-dose 9vHPV vaccine regimen. Three participants (1.5%) discontinued from the study due to protocol deviation or withdrawal by participant.

Table 2. Disposition of Subjects (Day 1 to Month 7).

	9vHPV Vaccine	
	n	(%)
Subjects in population	201	
Vaccinated at		
Vaccination 1	200	(99.5)
Vaccination 2	200	(99.5)
Vaccination 3	198	(98.5)
Status for Trial		
Completed	198	(98.5)
Discontinued	3	(1.5)
Protocol Deviation	1	(0.5)
Withdrawal By Subject	2	(1.0)
Status for Study Medication in Trial		
Started	200	
Completed	198	(99.0)
Discontinued	2	(1.0)
Withdrawal By Subject	2	(1.0)

Baseline data

The age and gender distribution of study population were as planned in study protocol.

Table 3. Subjects Characterized by Age Strata.

	9 to 15 Years of Age		16 to 26 Years of Age		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	101		100		201	
Gender						
Male	33	(32.7)	33	(33.0)	66	(32.8)
Female	68	(67.3)	67	(67.0)	135	(67.2)
Age (Years)						
9 to 12 Years of Age	50	(49.5)	0	(0.0)	50	(24.9)
13 to 15 Years of Age	51	(50.5)	0	(0.0)	51	(25.4)
16 to 26 Years of Age	0	(0.0)	100	(100.0)	100	(49.8)
Mean	12.3		19.3		15.8	
SD	2.1		3.0		4.4	
Median	13.0		19.0		15.0	
Range	9 to 15		16 to 26		9 to 26	
Race						
Asian	101	(100.0)	100	(100.0)	201	(100.0)

The study population was mainly HPV seronegative before vaccination.

Table 4. Baseline HPV serostatus at Day 1 (all randomised subjects)

HPV Type	9vHPV Vaccine (N=201)		
		Day 1 Serostatus	
	n	Positive m (%)	Negative m (%)
Anti-HPV 6	200	4 (2.0)	196 (98.0)
Anti-HPV 11	200	1 (0.5)	199 (99.5)
Anti-HPV 16	200	8 (4.0)	192 (96.0)
Anti-HPV 18	200	5 (2.5)	195 (97.5)
Anti-HPV 31	200	7 (3.5)	193 (96.5)
Anti-HPV 33	200	1 (0.5)	199 (99.5)
Anti-HPV 45	200	2 (1.0)	198 (99.0)
Anti-HPV 52	200	3 (1.5)	197 (98.5)
Anti-HPV 58	200	5 (2.5)	195 (97.5)

Percentages are calculated as 100*(m/n).
N = Number of subjects randomized.
n = Number of subjects with non-missing Day 1 anti-HPV cLIA results.
m = Number of subjects who are serostatus positive (or negative) at Day 1.
HPV = Human papillomavirus ; cLIA = Competitive Luminex immunoassay

Immunogenicity results

All participants in the HPV type-specific PPI population seroconverted for each of the HPV types by Month 7. The lower limit of the 95% CI of the seroconversion percentage was greater than 96% for each HPV type, which met the predefined statistical criterion (the lower limit of the 95% CI to be greater than 90%) for acceptable anti-HPV seroconversion.

Robust anti-HPV GMT responses were observed for all HPV types in each of the HPV type specific PPI population by Month 7 (4 weeks post-dose 3). In a subgroup analysis stratified by age, a trend towards higher GMTs was observed in 9 to 15-year old participants compared to 16 to 26-year old participants at Month 7 across the 9 HPV types.

Table 5. Summary of month 7 anti-HPV cLIA Geometric mean titres and seroconversion percentages by age strata (Per-protocol immunogenicity population)

	9vHPV Vaccine (N=200)					
		GMT (mMU/mL)			Seroconversion	
Assay (cLIA)	n	GMT	(95% CI)	m	Percent	(95% CI)
Anti-HPV 6						
9 to 15 Years of Age	98	1,203.1	(1,076.0, 1,345.2)	98	100%	(96.3%, 100%)
16 to 26 Years of Age	92	835.2	(731.1, 954.1)	92	100%	(96.1%, 100%)
Anti-HPV 11						
9 to 15 Years of Age	98	970.1	(863.2, 1,090.2)	98	100%	(96.3%, 100%)
16 to 26 Years of Age	92	645.3	(555.8, 749.2)	92	100%	(96.1%, 100%)
Anti-HPV 16						
9 to 15 Years of Age	98	5,579.0	(4,915.4, 6,332.1)	98	100%	(96.3%, 100%)
16 to 26 Years of Age	89	3,728.7	(3,209.6, 4,331.7)	89	100%	(95.9%, 100%)
Anti-HPV 18						
9 to 15 Years of Age	98	2,115.1	(1,833.9, 2,439.3)	98	100%	(96.3%, 100%)
16 to 26 Years of Age	92	1,221.8	(1,025.7, 1,455.4)	92	100%	(96.1%, 100%)
Anti-HPV 31						
9 to 15 Years of Age	97	1,458.4	(1,271.2, 1,673.2)	97	100%	(96.3%, 100%)
16 to 26 Years of Age	91	873.5	(740.5, 1,030.4)	91	100%	(96.0%, 100%)
Anti-HPV 33						
9 to 15 Years of Age	100	641.2	(564.2, 728.6)	100	100%	(96.4%, 100%)
16 to 26 Years of Age	94	396.2	(342.0, 459.0)	94	100%	(96.2%, 100%)
Anti-HPV 45						
9 to 15 Years of Age	99	752.4	(636.3, 889.7)	99	100%	(96.3%, 100%)
16 to 26 Years of Age	94	439.7	(371.4, 520.5)	94	100%	(96.2%, 100%)
Anti-HPV 52						
9 to 15 Years of Age	100	632.4	(551.0, 725.8)	100	100%	(96.4%, 100%)
16 to 26 Years of Age	92	388.6	(335.2, 450.6)	92	100%	(96.1%, 100%)
Anti-HPV 58						
9 to 15 Years of Age	98	888.9	(771.3, 1,024.5)	98	100%	(96.3%, 100%)
16 to 26 Years of Age	92	545.6	(466.3, 638.6)	92	100%	(96.1%, 100%)

†The per-protocol immunogenicity population includes all subjects who (1) received all planned vaccinations within acceptable day ranges, (2) provided Month 7 serology result within an acceptable day range, (3) were seronegative at Day 1 for the relevant HPV type(s), and (4) had no other protocol deviations that could interfere with the evaluation of immune response.

N = Number of subjects randomized who received at least 1 injection.

n = Number of subjects contributing to the analysis, m = Number of seropositive subjects.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Primary Immunogenicity Endpoint

- All participants in the PPI population seroconverted for each of the 9vHPV vaccine types (6, 11, 16, 18, 31, 33, 45, 48, and 58) by Month 7.
- The lower limit of the 95% CI of the seroconversion percentage was greater than 98% for each HPV vaccine type, such that the primary immunogenicity hypothesis was met.

Secondary Immunogenicity Endpoint

- Robust anti-HPV GMT responses were observed for all HPV vaccine types following the administration of 3 doses of 9vHPV.

Safety results

Approximately half of the participants reported at least 1 AE from Day 1 to Day 15 following vaccination. Nearly half of the participants (45.0%) had injection-site AEs, all of which were deemed vaccine related. Seventeen percent of participants had systemic AEs, the majority of which were not considered to be vaccine related.

Only 1 SAE was reported, which was not considered to be vaccine related. No participant died during the study. No participant discontinued vaccine due to AEs.

Similar observations were made for AEs reported between Day 1 to Month 7.

Table 6. AEs day 1-15 following any vaccination visit

	9vHPV Vaccine	
	n	(%)
Subjects in population with follow-up	200	
with one or more adverse events	101	(50.5)
injection-site	90	(45.0)
non-injection-site	34	(17.0)
with no adverse event	99	(49.5)
with vaccine-related† adverse events	90	(45.0)
injection-site	90	(45.0)
non-injection-site	2	(1.0)
with non-serious adverse events	100	(50.0)
with serious adverse events	1	(0.5)
with serious vaccine-related adverse events	0	(0.0)
who died	0	(0.0)
discontinued vaccine due to an adverse event	0	(0.0)
discontinued vaccine due to a vaccine-related adverse event	0	(0.0)
discontinued vaccine due to a serious adverse event	0	(0.0)
discontinued vaccine due to a serious vaccine-related adverse event	0	(0.0)

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

Table 7. Systemic AEs by System Organ Class (1-15 days after any vaccination visits)

	9vHPV Vaccine		
	n	(%)	Estimate (95% CI)†
Subjects in population with follow-up	200		
with one or more systemic adverse events	34	(17.0)	17.0 (12.1, 22.9)
with no systemic adverse events	166	(83.0)	83.0 (77.1, 87.9)
Ear and labyrinth disorders	**1**	**(0.5)**	**0.5 (0.0, 2.8)**
Deafness unilateral	1	(0.5)	0.5 (0.0, 2.8)
Gastrointestinal disorders	**6**	**(3.0)**	**3.0 (1.1, 6.4)**
Abdominal pain	1	(0.5)	0.5 (0.0, 2.8)
Abdominal pain upper	1	(0.5)	0.5 (0.0, 2.8)
Diarrhoea	1	(0.5)	0.5 (0.0, 2.8)
Dyspepsia	1	(0.5)	0.5 (0.0, 2.8)
Haematochezia	1	(0.5)	0.5 (0.0, 2.8)
Nausea	1	(0.5)	0.5 (0.0, 2.8)
General disorders and administration site conditions	**3**	**(1.5)**	**1.5 (0.3, 4.3)**
Fatigue	1	(0.5)	0.5 (0.0, 2.8)
Feeling hot	1	(0.5)	0.5 (0.0, 2.8)
Pyrexia	1	(0.5)	0.5 (0.0, 2.8)
Infections and infestations	**7**	**(3.5)**	**3.5 (1.4, 7.1)**
Nasopharyngitis	5	(2.5)	2.5 (0.8, 5.7)
Pharyngitis	2	(1.0)	1.0 (0.1, 3.6)
Subcutaneous abscess	1	(0.5)	0.5 (0.0, 2.8)
Injury, poisoning and procedural complications	**2**	**(1.0)**	**1.0 (0.1, 3.6)**
Limb injury	1	(0.5)	0.5 (0.0, 2.8)
Post procedural inflammation	1	(0.5)	0.5 (0.0, 2.8)
Musculoskeletal and connective tissue disorders	**6**	**(3.0)**	**3.0 (1.1, 6.4)**
Arthralgia	1	(0.5)	0.5 (0.0, 2.8)
Arthritis	1	(0.5)	0.5 (0.0, 2.8)
Muscle fatigue	2	(1.0)	1.0 (0.1, 3.6)
Musculoskeletal pain	2	(1.0)	1.0 (0.1, 3.6)
Neck pain	1	(0.5)	0.5 (0.0, 2.8)
Nervous system disorders	**9**	**(4.5)**	**4.5 (2.1, 8.4)**
Dizziness	5	(2.5)	2.5 (0.8, 5.7)
Headache	7	(3.5)	3.5 (1.4, 7.1)
Respiratory, thoracic and mediastinal disorders	**5**	**(2.5)**	**2.5 (0.8, 5.7)**
Cough	1	(0.5)	0.5 (0.0, 2.8)
Epistaxis	1	(0.5)	0.5 (0.0, 2.8)
Upper respiratory tract inflammation	3	(1.5)	1.5 (0.3, 4.3)
Skin and subcutaneous tissue disorders	**3**	**(1.5)**	**1.5 (0.3, 4.3)**
Acne	1	(0.5)	0.5 (0.0, 2.8)
Dermatitis allergic	1	(0.5)	0.5 (0.0, 2.8)
Swelling face	1	(0.5)	0.5 (0.0, 2.8)

† Based on Clopper-Pearson method.

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence meets the incidence criterion in the report title, after rounding.

The same subject may appear in different system organ classes.

Safety Results Summary

- The most common AE was injection-site pain (44.5%).

- The incidence of systemic AEs and vaccine-related systemic AEs was low (17.0% and 1.0%, respectively).
- Most injection-site and systemic AEs were mild in intensity.
- One SAE was reported, which was not considered vaccine related.
- No participant discontinued vaccine due to AEs.
- No participant had a temperature elevation of ≥37.8°C (100.0°F) during the 5 days following any vaccination visit.

2.3.3. **Discussion on clinical aspects**

This study (V503-017) was designed to evaluate the safety and immunogenicity of the 9vHPV vaccine in 9 to 26-year-old male and female participants in order to support licensure in Vietnam.

Compliance with the study protocol was good. Overall, of the 201 participants enrolled in this study, 198 (98.5%) of participants completed the study.

Immunogenicity

The 9vHPV vaccine elicited a 100% seroconversion rate in this study with all baseline seronegative participants who received the vaccine by Month 7 (4 weeks post-dose 3) for each of the HPV types. The vaccine was highly immunogenic as demonstrated by robust antibody responses to all vaccine types following administration of a 3-dose regimen of the 9vHPV vaccine.

Robust anti-HPV GMT responses observed in this study suggest that the HPV antibody levels observed in V503-017 are sufficient to generate protection against HPV infection and disease in the Vietnamese population. The trend of higher GMTs in the younger age group compared to the older age group observed in this study is consistent to those observed in global studies of the 9vHPV vaccine.

Safety

Administration of 9vHPV vaccine was generally well tolerated among study participants. About half of the participants in the study had vaccine-related injection-site pain, most of which were mild in intensity. No participant in the study experienced any vaccine related SAE. Only 2 participants had vaccine related systemic AEs, which resolved completely.

The safety findings in this study were generally comparable to the tolerability findings reported for several other international 9vHPV vaccine studies.

The study population was relatively small (N= 201) and including only small fraction of children at age 9 to 15 (N=101) and therefore the chance to detect rare AEs and SAEs is low. No new safety concern is raised from this study. In conclusion, the 9vHPV vaccine was highly immunogenic and well tolerated in both male and female study participants, 9 to 26 years of age in Vietnam.

3. Rapporteur's overall conclusion and recommendation

The results of this study indicate no new efficacy or safety concern. The P46 procedure is considered fulfilled. No further regulatory action required.