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Procedure Management and Committees Support Division

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

Cervarix

human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Procedure no: EMEA/H/C/000721/P46/088

Note

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

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1. Introduction

On 7 September 2015, the MAH submitted the immunogenicity and safety results of study HPV-071 from Month 18 up to Month 24 for Cervarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

HPV-071 is a paediatric study documenting immunogenicity and safety of Cervarix in healthy **females aged 9-14 years in a 2-dose schedule** vs. Gardasil administered in a 2-dose and in a 3-dose (ELISA).

Analyses were performed as planned in the protocol except that the Pseudovirion-Based Neutralization Assay (PBNA) analysis was not performed at the Month 24 time point. Results for this assay at Month 24 will be presented in the CSR written for the next time point (Month 36).

2.2. Information on the pharmaceutical formulation used in the study

Cervarix and the placebo vaccine (Al(OH)3) were developed and manufactured by GSK Biologicals.

The comparator vaccine, Gardasil, was licensed by Merck & Co in all countries participating in this study.

Table 1. Study vaccines.

Treatment name	Vaccine name	Formulation	Presentation	Volume*	Number of doses	Lot number
HPV-16/18	HPV-16/18 L1 VLP AS04 vaccine	Each 0.5 ml dose contains: - 20 µg HPV-16 L1 VLP - 20 µg HPV-18 L1 VLP - 50 µg MPL - 0.5 mg aluminium as $Al(OH)_3$ - 8 mM sodium dihydrogen phosphate dehydrate - 150 mM sodium choloride - water for injection	Liquid in pre-filled syringes	0.6 ml	2	AHPVA144B AHPVA133C AHPVA133E AHPVA151C AHPVA184C AHPVA177D
HPV-6/11/16/18	quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine	Each 0.5 ml dose contains: - 40 µg HPV-16 L1 proteins - 20 µg HPV-18 L1 proteins - 20 µg HPV-6 L1 proteins - 40 µg HPV-11 L1 proteins - 225 µg aluminium hydroxyphosphate	Liquid in pre-filled syringes	0.6 ml	2 or 3**	NP39130 H006966
Placebo	$Al(OH)_3$	Each 0.5 ml dose contains: - 0.5 mg aluminium as $Al(OH)_3$ - water for injection	Liquid in pre-filled syringes	0.6 ml	1***	PHPVA012A

VLP: Virus-like Particles; L1 = structural protein of HPV; MPL = 3-O-desacyl-4'-monophosphoryl lipid A
$Al(OH)_3$ = aluminium hydroxide, ml = millilitre, µg = microgram
* Injectable volume = 0.5 mL
** The total number of doses is 2 or 3 depending on the study group (Gard_2D or Gard_3D)
*** Administered in the 2-dose groups (HPV_2D and Gard_2D) at Month 2 to maintain the study observer-blind

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an interim report for:

• Study 115411 (HPV-071), a Phase IIIb observer-blind, randomized, multicentre primary immunization study to evaluate the immunogenicity and safety of Cervarix (bivalent HPV-16/18 L1 VLP AS04-adjuvanted) and Gardasil (quadrivalent HPV-6/11/16/18 aluminium-adjuvanted), when administered intramuscularly according to alternative 2-dose schedules in 9-14 year old healthy females.

2.3.2. Clinical study

Description

HPV-071 is an ongoing Phase IIIb observer-blind, randomized, multi-centre trial (Sweden, Hong Kong, France and Singapore).

Methods

Objectives

Primary objective

Immunogenicity

- The primary objective of the trial was to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix was non-inferior/superior to that of Gardasil after administration according to a 2-dose schedule at 0, 6 months in 9-14 years old females, one month after the last dose (Month 7).
  If non-inferiority at Month 7 was shown, non-inferiority/superiority analysis by comparison of the immune response to both vaccine antigens between the Cervarix 2-dose group and the Gardasil 2-dose group at Months 12, 18, 24 and 36 will be performed (first secondary objective).

Secondary objective

Immunogenicity

- If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of a **2-dose Cervarix** schedule is non-inferior/superior to that of a **2-dose Gardasil** schedule, both administered at 0, 6 months, at Months 12, 18, 24 and 36.
- If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of a **2-dose Cervarix** schedule at 0, 6 months is non-inferior/superior to that of a **3-dose Gardasil** schedule at 0, 2, 6 months at Months 7, 12, 18, 24 and 36.
- To assess the immune responses to HPV types 16 and 18 by ELISA at Day 0 and Months 7, 12, 18, 24 and 36 in all subjects.
- To assess the immune responses to HPV types 16 and 18 by PBNA in a subset of subjects at Day 0 and Months 7, 12, 18, 24 and 36.

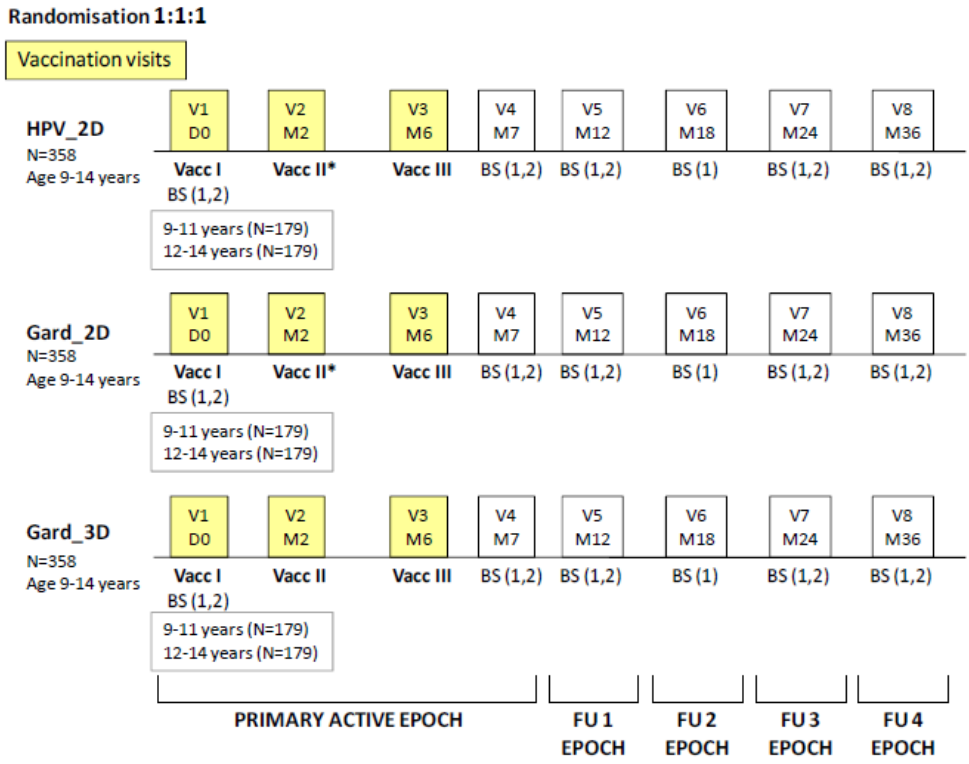
- To assess cell-mediated immunity (CMI), i.e., T-cell-mediated and memory B-cell immune responses specific to HPV-16 and HPV-18 in a sub-cohort of subjects at Day 0, Months 7, 12, 24 and 36.

Safety

- To assess the reactogenicity of the administered vaccines in all groups after each dose.
- To assess the safety of the administered vaccines in all groups.
- To evaluate compliance with completion of vaccination in all groups.

Study design

HPV-071 is a Phase IIIb, observer-blind, randomised, age-stratified, multicentre study with 3 parallel groups.



N = number of subjects; V = Visit; D = Day; M = Month; Vacc = Vaccination
BS (1) = blood sample for immunogenicity (assessment of ELISA in all subjects and PBNA in a subset of subjects)
BS (2) = blood sample for CMI in a sub-cohort of subjects
FU = follow-up
* Subjects in the 2-dose groups received placebo ($Al(OH)_3$ at Visit 2 (Vacc II) to maintain the study as observer-blind.
The results of the analyses conducted on data collected during the follow-up epochs are being/ will be reported in annex reports.

Study population

Inclusion criteria

- A healthy female between, and including, 9 and 14 years of age at the time of the first vaccination, and whose parent(s)/ LAR(s) in the opinion of the investigator, could and would comply with the requirements of the protocol and from whom written informed consent/ written assent was obtained were included in the study.

- Females of non-child bearing potential or of child bearing potential practicing adequate contraception for the given time and having a negative pregnancy test on the day of vaccination were enrolled

Inclusion criteria

- Previous vaccination against HPV or previous administration of MPL or ASO4, planned administration against HPV outside the scope of the study, planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days (i.e., Day 0-29) of each dose of the vaccine with the exception of a few vaccines.
- A woman planning to become pregnant, likely to become pregnant (as determined by the investigator) or planning to discontinue contraceptive precautions.
- Use of any investigational or non-registered product (other than study vaccine), chronic administration of immunosuppresants, immunodeficient or immunosuppressant condition and history of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine including latex.

Sample size

Of the 1075 subjects vaccinated in the study, **1052 subjects** completed the Month 18 visit and 1048 subjects completed the Month 24 visit.

Table 1. Number of subjects vaccinated, completed and withdrawn with reason for withdrawal up to Month 18 (Total vaccinated cohort).

	HPV_2D	Gard_2D	Gard_3D	Total
Number of subjects vaccinated	359	358	358	1075
Number of subjects completed	356	347	349	1052
Number of subjects withdrawn	3	11	9	23
Reasons for withdrawal :				
Subject died	0	0	0	0
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	2	8	3	13
Migrated/moved from study area	0	1	1	2
Lost to follow-up (subjects with incomplete and complete vaccination course)	1	2	5	8
Sponsor study termination	0	0	0	0
Others	0	0	0	0

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit

Table 2. Number of subjects vaccinated, completed and withdrawn with reason for withdrawal up to Month 24 (Total vaccinated cohort).

	HPV_2D	Gard_2D	Gard_3D	Total
Number of subjects vaccinated	359	358	358	1075
Number of subjects completed	355	344	349	1048
Number of subjects withdrawn	4	14	9	27
Reasons for withdrawal :				
Subject died	0	0	0	0
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	2	8	3	13
Migrated/moved from study area	*2*	*2*	*2*	2
Lost to follow-up (subjects with incomplete and complete vaccination course)	2	4	6	12
Sponsor study termination	0	0	0	0
Others	0	0	0	0

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come back for the last visit
n = number present in one group only, and duplicated to avoid unblinding

Treatments

Treatment groups

- 3 parallel groups
    - Cervarix according to a 2-dose schedule (0, 6 months)
    - Gardasil according to a 2-dose schedule (0, 6 months)
    - Gardasil according to a 3-dose schedule (0, 2, 6 months)
- The two groups vaccinated according to the 2-dose schedule received one dose of placebo at Month 2 to maintain study blind (observer-blind).

Endpoints

Primary endpoint

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and antibody titres assessed by ELISA one month after the last dose of study vaccine (Month 7).

Secondary endpoints

Immunogenicity

- Anti-HPV-16/18 seroconversion rates and antibody titres assessed by ELISA at Day 0 and Months 12, 18, 24 and 36.
- Anti-HPV-16/18 seroconversion rates and antibody titres assessed by PBNA in a subset of subjects at Day 0 and Months 7, 12, 18, 24 and 36.
- T-cell and B-cell-mediated immune responses (frequency of cytokine(s)-positive CD4 or CD8 T lymphocytes and frequency of HPV-specific memory B-cells) in the sub-cohort for CMI at Day 0 and Months 7, 12, 24 and 36.

Safety

- The occurrence and intensity of solicited local symptoms during the 7-day period (Days 0-6) following each vaccination in all groups.

- The occurrence, intensity and causal relationship to vaccination of solicited general symptoms during the 7-day period (Days 0-6) following each vaccination in all groups.
- The occurrence, intensity and causal relationship to vaccination of unsolicited symptoms during the 30-day period (Days 0-29) following each vaccination in all groups.
- The occurrence of pIMDs from first vaccination to six months after the last vaccine dose (from Day 0 up to Month 12) in all groups.
- The occurrence of MSCs throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of SAEs throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of SAEs related to the investigational product, to study participation, to GSK concomitant products or any fatal SAE throughout the study period (from Day 0 up to Month 36) in all groups.
- The occurrence of pregnancies and pregnancy outcomes throughout the study period (from Day 0 up to Month 36) in all groups.
- Use of concomitant medication (e.g. prophylactic use of antibiotics or antipyretics) throughout the study period (from Day 0 up to Month 36) in all groups.
- The percentage of subjects completing the vaccination schedule in all groups.

Statistical Methods

Comparison between groups

- Primary between-group comparisons to assess the non-inferiority at Month 7 were performed in the ATP cohort for immunogenicity on subjects seronegative by ELISA at Day 0 for the antigen under analysis. Subjects seropositive for only one antigen were eliminated for the analysis of that antigen but were still evaluable for the analysis of the other antigen. In addition, non-inferiority assessment was also performed in the TVC on all subjects (regardless of serostatus at Day 0).
- Between-group comparisons to assess superiority were performed in the TVC on all subjects (regardless of serostatus at Day 0). In addition, superiority assessment was also performed in the ATP cohort for immunogenicity on subjects seronegative at Day 0 for the antigen under analysis.

Criteria for non-inferiority

- Non-inferiority with respect to seroconversion rates was shown if, one month after the last dose, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% CI for the difference (Gardasil minus Cervarix) was below 5%.
- Non-inferiority with respect to GMT for both anti-HPV-16 and anti-HPV-18 antibodies was shown if, one month after the last dose, the upper limit of the 95% CI for the GMT ratio (Gardasil divided by Cervarix) was below 2.

Criteria for superiority

- If non-inferiority was reached, and if the lower limit of the two-sided 95% CI for the ratio of GMTs Cervarix divided by Gardasil of a given antigen was above 1 in the ATP cohort for immunogenicity, the following criteria for superiority were to be assessed sequentially in the

TVC:

- First, superiority for HPV-18 was assessed. Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-18 antibodies (Cervarix divided by Gardasil) was above 1 with the associated p-value.
- Second, if superiority for HPV-18 is shown, superiority for HPV-16 was assessed. Superiority was shown if the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 antibodies (Cervarix divided by Gardasil) was above 1 with the associated p-value.

Demographic characteristics

- In the ATP cohort, the age at vaccination was comparable between the different groups (11.5 ± 1.62 years in Cervarix group, 11.5 ± 1.55 years in Gardasil 2-dose group and 11.6 ± 1.63 years in Gardasil 3-dose group).
- The three groups had a comparable ethnical/racial distribution, with an approximate 50% of the subjects in each group of East Asian heritage and an approximate 25% of Caucasian heritage. Demographic characteristics in the TVC were similar.

Results

Efficacy results

- *HPV-16/18 serostatus at baseline*

The majority of subjects was initially seronegative for both HPV-16 and HPV-18, i.e., 96% in all groups (Table 1).

Table 1. Seropositivity status at Baseline (ATP cohort for immunogenicity)

		HPV_2D (N = 337)		Gard_2D (N = 334)		Gard_3D (N = 334)	
Anti-HPV-16	**Anti-HPV-18**	**n**	**%**	**n**	**%**	**n**	**%**
P	N	7	2.1	7	2.1	12	3.6
N	P	3	0.9	3	0.9	1	0.3
N	N	327	97	324	97	321	96.1

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
P=Positive
N=Negative

- *Non-inferiority analysis on primary objective (Cervarix 2-dose vs Gardasil 2-dose, **Month 18**)*

The non-inferiority assessment of seroconversion rates is presented in Table 2 and the non-inferiority assessment of anti-HPV-16 and anti-HPV-18 antibody GMT (ELISA) is presented in Table 3.

Table 2. Non-Inferiority assessment of seroconversion rates one month after the last dose (Month 18) in initially seronegative subjects (ATP cohort for immunogenicity)

						Difference in seroconversion rate (Group 2 minus Group 1)			
								95 % CI	
Group 1	N	%	Group 2	N	%	Difference	%	LL	UL
HPV_2D	322	100	Gard_2D	320	99.7	Gard_2D - HPV_2D	-0.31	-1.75	0.87

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
N = number of subjects with available results
% = percentage of subjects with HPV-16 titre ≥ 19 EU/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the difference in seroconversion rates (Gardasil minus Cervarix) is below 5%.

Table 3. Non-Inferiority assessment of anti-HPV-16 and anti-HPV-18 immune response one month after the last dose (**Month 18**) in initially seronegative subjects (ATP cohort for immunogenicity)

					GMT ratio (Gard_2D / HPV_2D)		
	Gard_2D		HPV_2D			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-HPV-16	320	674.7	322	1499.4	0.45	0.39	0.52
anti-HPV-18	324	133.1	327	762.2	0.17	0.15	0.21

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
GMT = geometric mean antibody titre
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the GMT ratio (Gardasil 2-dose schedule divided by Cervarix 2-dose schedule) is below 2.

- *Superiority analysis on primary objective (Cervarix 2-dose vs Gardasil 2-dose, **Month 18**)*

Because non-inferiority was reached, and the lower limit of the two-sided 95% CI for the ratio of GMTs Cervarix divided by Gardasil of a given antigen was above 1 in the ATP cohort for immunogenicity, a superiority analysis was performed.

Table 4. Superiority assessment of immune response one month after the last dose (Month 18) (Total Vaccinated cohort)

Antibody	***Cervarix* 2-dose**		***Gardasil* 2-dose**		**GMT ratio (*Cervarix / Gardasil*)**		
						95% CI	
	N	**GMT**	**N**	**GMT**	**Value**	**LL**	**UL**
HPV-16	354	1467.8	346	670.0	2.19	1.90	2.53
HPV-18	354	750.8	346	132.2	5.68	4.86	6.64

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit p-value= 0.0001

The superiority criterion was met as the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 and anti HPV-18 antibodies (Cervarix 2-dose schedule divided by Gardasil 2-dose schedule) is above 1.

CHMP's comment

The primary objective of the study was met.

After Cervarix vaccination as compared to Gardasil vaccination, both administered according to a 2-dose schedule in females aged 9-14 years of age, study HPV-071 demonstrated **at Month 18**

- Non-inferiority in terms of seroconversion rates; and
- Superiority in terms of GMT ratio in the Total Vaccinated cohort.

• *Superiority analysis on primary objective (Cervarix 2-dose vs Gardasil 2-dose, **Month 24**)*

Table 5. Superiority assessment of immune response one month after the last dose (Month 24) (Total Vaccinated cohort)

Antibody	*Cervarix* 2-dose		*Gardasil* 2-dose		GMT ratio (*Cervarix* / *Gardasil*)		
						95% CI	
	N	GMT	N	GMT	Value	LL	UL
HPV-16	350	1263.5	347	613.8	2.06	1.81	2.35
HPV-18	350	611.5	347	175.3	3.49	2.97	4.10

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit p-value= 0.0001

The superiority criterion was met as the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 and anti HPV-18 antibodies (Cervarix 2-dose schedule divided by Gardasil 2-dose schedule) is above 1.

CHMP's comment

After Cervarix vaccination as compared to Gardasil vaccination, both administered according to a 2-dose schedule in females aged 9-14 years of age, study HPV-071 demonstrated **at Month 24**

- Superiority in terms of GMT ratio in the Total Vaccinated cohort.

• *Non-inferiority analysis on secondary objective (Cervarix **2-dose** vs Gardasil **3-dose**, **Month 18**)*

The secondary objective, i.e. to evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix administered according to a 2-dose schedule at 0, 6 months was non-inferior/superior to that of Gardasil vaccine administered according to the standard 3-dose schedule (0, 2, 6 months) at Month 18, was also met for this study.

Table 6. Non-Inferiority assessment of seroconversion rates one month after the last dose (**Month 18**) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	*Cervarix* 2-dose		*Gardasil* 3-dose		Difference in seroconversion rate (*Gardasil* minus *Cervarix*)			
							95 % CI	
	N	%	N	%	Difference	%	LL	UL
HPV-16	322	100	318	100	*Gardasil* minus *Cervarix*	0.00	-1.20	1.18
HPV-18	327	100	329	97.6	*Gardasil* minus *Cervarix*	-2.43	-4.73	-1.24

N = number of subjects with available results
% = percentage of subjects with anti-HPV-16 antibody concentration ≥ 19 EU/ml; percentage of subjects with anti-HPV-18 antibody concentration ≥ 18 EU/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the difference in seroconversion rates (Gardasil minus Cervarix) is below 5%.

Table 7. Non-Inferiority assessment of anti-HPV-16 and anti-HPV-18 immune response one month after the last dose (**Month 18**) in initially seronegative subjects (ATP cohort for immunogenicity)

					GMT ratio (Gard_3D / HPV_2D)		
	Gard_3D		HPV_2D			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-HPV-16	318	818.0	322	1499.4	0.55	0.48	0.62
anti-HPV-18	329	230.0	327	762.2	0.30	0.26	0.36

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
GMT = geometric mean antibody titre
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the GMT ratio (Gardasil 3-dose schedule divided by Cervarix 2-dose schedule) is below 2.

- *Superiority analysis on secondary objective (Cervarix **2-dose** vs Gardasil **3-dose**, **Month 18**)*

Because non-inferiority was reached, and the lower limit of the two-sided 95% CI for the ratio of GMTs Cervarix divided by Gardasil of a given antigen was above 1 in the ATP cohort for immunogenicity, a superiority analysis was performed.

Table 8. Superiority assessment of immune response one month after the last dose (Month 18) (Total Vaccinated cohort)

Antibody	***Cervarix* 2-dose**		***Gardasil* 3-dose**		**GMT ratio (*Cervarix / Gardasil*)**		
						95% CI	
	N	**GMT**	**N**	**GMT**	**Value**	**LL**	**UL**
HPV-16	354	1467.8	349	808.3	1.82	1.60	2.07
HPV-18	354	750.8	349	228.1	3.29	2.80	3.86

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit p-value= 0.0001

The superiority criterion was met as the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 and anti HPV-18 antibodies (Cervarix 2-dose schedule divided by Gardasil 3-dose schedule) is above 1.

CHMP's comment

After a **2-dose Cervarix** vaccination as compared to a **3-dose Gardasil** vaccination in females aged 9-14 years of age, study HPV-071 demonstrated **at Month 18**

- Non-inferiority in terms of seroconversion rates; and
- Superiority in terms of GMT ratio in the Total Vaccinated cohort.

- *Non-inferiority analysis on secondary objective (Cervarix **2-dose** vs Gardasil **3-dose**, **Month 24**)*

Table 9. Non-Inferiority assessment of anti-HPV-16 and anti-HPV-18 immune response one month after the last dose (**Month 24**) in initially seronegative subjects (ATP cohort for immunogenicity)

					GMT ratio (Gard_3D / HPV_2D)		
	Gard_3D		HPV_2D			95% CI	
Antibody	N	GMT	N	GMT	Value	LL	UL
anti-HPV-16	312	631.9	318	1304.3	0.48	0.43	0.55
anti-HPV-18	323	181.6	321	626.9	0.29	0.25	0.34

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
GMT = geometric mean antibody titre
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the GMT ratio (Gardasil 3-dose schedule divided by Cervarix 2-dose schedule) is below 2.

Table 10. Non-Inferiority assessment of seroconversion rates one month after the last dose (**Month 24**) in initially seronegative subjects (ATP cohort for immunogenicity)

Antibody	***Cervarix* 2-dose**		***Gardasil* 3-dose**		**Difference in seroconversion rate (*Gardasil* minus *Cervarix*)**			
							95 % CI	
	N	**%**	**N**	**%**	**Difference**	**%**	**LL**	**UL**
HPV-16	318	100	312	100	*Gardasil* minus *Cervarix*	0.00	-1.22	1.20
HPV-18	321	100	323	96.6	*Gardasil* minus *Cervarix*	-3.41	-6.00	-1.91

N = number of subjects with available results
% = percentage of subjects with anti-HPV-16 antibody concentration ≥ 19 EU/ml; percentage of subjects with anti-HPV-18 antibody concentration ≥ 18 EU/ml
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

The non-inferiority criterion was met as the upper limit of the 95% CI for the difference in seroconversion rates (Gardasil minus Cervarix) is below 5%.

- *Superiority analysis on secondary objective (Cervarix **2-dose** vs Gardasil **3-dose**, **Month 24**)*

A superiority analysis was performed because non-inferiority was reached.

Table 7. Superiority assessment of immune response one month after the last dose (Month 24) (Total Vaccinated cohort)

Antibody	***Cervarix* 2-dose**		***Gardasil* 3-dose**		**GMT ratio (*Cervarix* / *Gardasil*)**		
						95% CI	
	N	**GMT**	**N**	**GMT**	**Value**	**LL**	**UL**
HPV-16	350	1263.5	347	613.8	2.06	1.81	2.35
HPV-18	350	611.5	347	175.3	3.49	2.97	4.10

GMT = geometric mean antibody titre
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit p-value= 0.0001

The superiority criterion was met as the lower limit of the 95% CI for the ratio of GMTs for anti-HPV-16 and anti HPV-18 antibodies (Cervarix 2-dose schedule divided by Gardasil 3-dose schedule) is above 1.

CHMP's comment

After a **2-dose Cervarix** vaccination as compared to a **3-dose Gardasil** vaccination in females aged 9-14 years of age, study HPV-071 demonstrated **at Month 24**

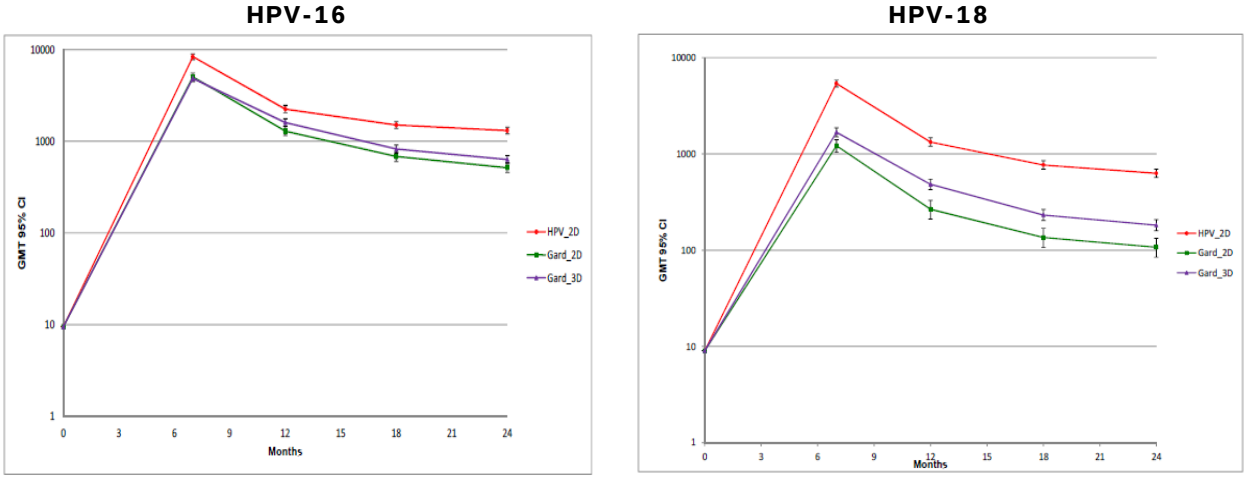
- Non-inferiority in terms of seroconversion rates; and

- Superiority in terms of GMT ratio in the Total Vaccinated cohort.

- *Persistence of HPV antibody titres (Cervarix 2-dose vs Gardasil 2-dose or 3-dose)*

GMTs for antibodies against both HPV-16 and HPV-18, which had reached a peak response at Month 7, showed a continuous decline thereafter in all three groups, but remained higher in the Cervarix group as compared to both Gardasil groups at Month 24 (Figure 3). This is in line with previous observations.

Figure 1. Persistence of HPV-16/18 antibody titres (ELISA) in subjects seronegative at baseline (Month 24 ATP cohort for immunogenicity).



- *Anti-HPV-16/18 neutralising antibodies measured by PBNA at Month 18*

Pseudovirion-based neutralization assays (PBNA) for anti-HPV-16 and anti-HPV-18 was performed on a subset of 100 randomly selected subjects for each study group.

- All initially seronegative subjects in HPV_2D group and at least 97.8% of subjects in the Gard_2D and Gard_3D groups had seroconverted for anti-HPV-16 neutralising antibodies when measured by PBNA.
- All initially seronegative subjects in HPV_2D group had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA. In Gard_2D group, 88.0% of subjects and in Gard_3D group, 97.8% of subjects had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA.
- GMT levels for neutralizing antibodies against both HPV-16 and HPV-18, which had reached a peak response at Month 7, showed a further decline at Month 18 in all three groups.

- *Anti-HPV-16/18 neutralising antibodies measured by PBNA at Month 24*

Analyses were performed as planned in the protocol except that the Pseudovirion-Based Neutralization Assay (PBNA) analysis was not performed at the Month 24 time point. Results for this assay at Month 24 will be presented in the CSR written for the next time point (Month 36).

- *T-cell-mediated immune responses*

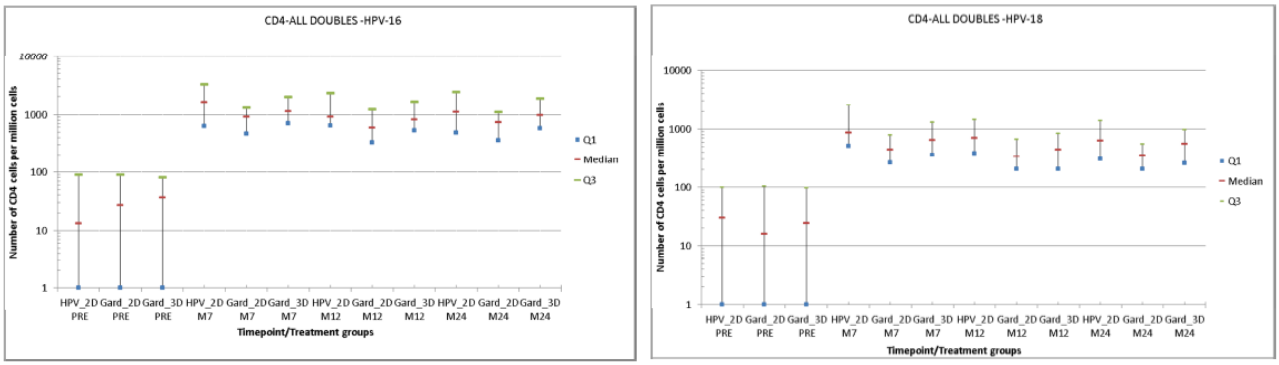
CD4+ T cell response

At Month 24, CD4+ T cells response (in terms of median frequency of HPV-16/18 antigen-specific

CD4+ T cells per million CD4+ T cells expressing at least two different immune markers [all doubles]) were as presented in Figure

Figure 4. CD4+ all doubles response by intracellular cytokine staining to HPV-16/18 (Month 24 ATP cohort for immunogenicity)

HPV-16 **HPV-18**



CD8+ T cell response

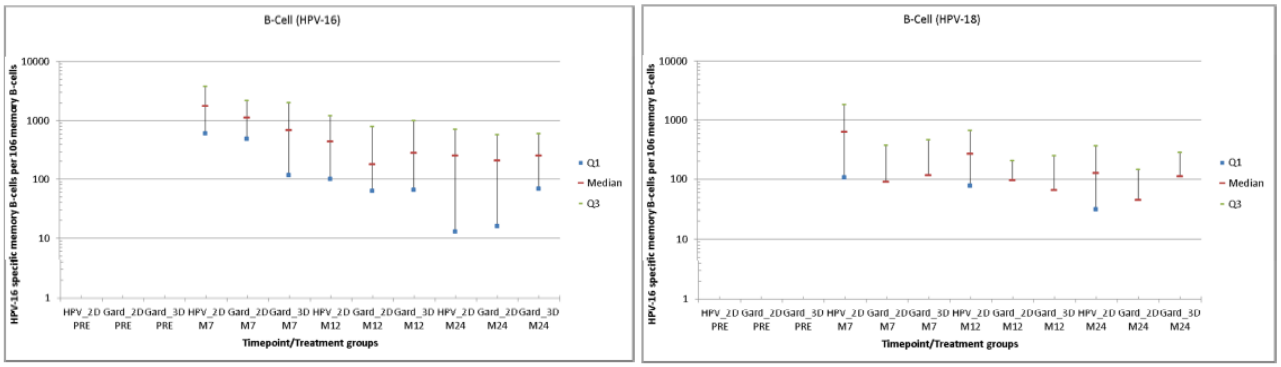
As observed in the previous time points, HPV-16 and HPV-18 specific CD8+ T cells response was undetectable (1.0 cell per million CD8+ T cells) in all three groups at Month 24.

- *Memory B-cell-mediated immune responses*

At Month 24, B cells response (in terms of median frequency of HPV-16/18 antigenspecific memory B cells per million memory B cells in subjects with detectable B cells) was as presented in Figure 5

Figure 5. B-cell elispot response to HPV-16/18 (Month 24 ATP cohort for immunogenicity)

HPV-16 **HPV-18**



Safety results

- *Serious adverse events up to Month 24*

One fatal case due to committed suicide was reported between the Month 24 study completion date

and the DLP for this CSR. The investigator considered this event as not related to study vaccine.

There were no adverse events that led to premature discontinuation of the study from Month 12 to Month 24.

More SAEs were reported for Cervarix over the entire study period up until Month 24, as well as in the period between Month 18 and Month 24, as shown in Tables 8 and 9 below.

Table 8. Global Summary of SAEs from Month 0 - Month 24 (Month 24 Total Vaccinated cohort)

	Group			
	HPV_2D	Gard_2D	Gard_3D	Total
Number of subjects with at least one SAE reported	18	5	6	29
Number of doses followed by at least one SAE	18	5	6	29
Number of SAEs classified by MedDRA Preferred Term*	21	5	8	34
Number of SAEs reported**	21	5	8	34

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once
** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once
SAE =Serious adverse event
n = number present in one group only, and duplicated to avoid unblinding

Table 9. Global Summary of SAEs from Month 18 – Month 24 (Month 24 Total Vaccinated cohort)

	Group			
	HPV_2D	Gard_2D	Gard_3D	Total
Number of subjects with at least one SAE reported	2	1	2	5
Number of doses followed by at least one SAE	2	1	2	5
Number of SAEs classified by MedDRA Preferred Term*	4	1	2	7
Number of SAEs reported**	4	1	2	7

HPV_2D = Subjects who received 2 doses of HPV-16/18 L1 VLP AS04 vaccine
Gard_2D = Subjects who received 2 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
Gard_3D = Subjects who received 3 doses of quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once
** Symptoms reported by a subject after a given dose and classified by the same Preferred Term and the same start date of the event, are counted once
SAE =Serious adverse event
n = number present in one group only, and duplicated to avoid unblinding

None of these SAEs were considered by the investigator to have a possible causal relationship to vaccination. All SAEs resolved without sequelae except for the SAEs - colitis ulcerative, anaphylactic reaction and juvenile idiopathic arthritis which were resolving at the time of the data lock point of this study.

2.3.3. Discussion on clinical aspects

Non-inferiority and superiority of immune responses to both HPV-16 and HPV-18 antigens was demonstrated at Month 18 and Month 24 when Cervarix was administered according to a 2-dose schedule at 0,6 months in 9-14 year old females versus Gardasil administered according to a 2-dose schedule at 0, 6 months or according to a 3-dose schedule at 0,2,6 months.

Both vaccines were generally well tolerated when administered according to a 3-dose or 2-dose schedule in subjects aged 9-14 years. However, **more SAEs** were reported in the 2-dose Cervarix group over the entire study period up until Month 24, as well as in the period between Month 18 and Month 24, compared to the Gardasil groups, regardless of the number of Gardasil doses.

3. CHMP's overall conclusion and recommendation

Overall conclusion

The Article 46 paediatric submission is considered fulfilled, and no further regulatory action is needed. The provided data do not cause concern regarding efficacy or safety of Cervarix.

The benefit/risk balance of Cervarix remains positive.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.