26 January 2017
EMA/100669/2017
Human Medicines Evaluation 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/P46/091

## Note

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

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# Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, the Company hereby submits the clinical study report HPV-071, Month 36 data, entitled: " A Phase IIIb observer-blind, randomized, multicentre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine and Merck's Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, when administered intramuscularly according to alternative 2-dose schedules in 9-14 year old healthy females.

Study reports for Month 7, dated 23 May 2014, and Month 12, dated 11 February 2015, were previously submitted under Article 46 of the regulation 1901/2006 on 12 March 2015 (as part of the variation II/67, eCTD sequence 0192). The Annex study report for Month 18 & Month 24, dated 13 August 2015, was previously submitted under Article 46 of the regulation 1901/2006 on 07 September 2015 (eCTD sequence 0207).

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.

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:<br>- 20 µg HPV-16 L1 VLP<br>- 20 µg HPV-18 L1 VLP<br>- 50 µg MPL<br>- 0.5 mg aluminium as $Al(OH)_3$<br>- 8 mM sodium dihydrogen phosphate dehydrate<br>- 150 mM sodium choloride<br>- water for injection | Liquid in pre-filled syringes | 0.6 ml | 2 | AHPVA144B<br>AHPVA133C<br>AHPVA133E<br>AHPVA151C<br>AHPVA184C<br>AHPVA177D |
| HPV-6/11/16/18 | quadrivalent HPV (HPV-6/11/16/18 L1 VLP) recombinant vaccine | Each 0.5 ml dose contains:<br>- 40 µg HPV-16 L1 proteins<br>- 20 µg HPV-18 L1 proteins<br>- 20 µg HPV-6 L1 proteins<br>- 40 µg HPV-11 L1 proteins<br>- 225 µg aluminium hydroxyphosphate | Liquid in pre-filled syringes | 0.6 ml | 2 or 3** | NP39130<br>H006966 |
| Placebo | $Al(OH)_3$ | Each 0.5 ml dose contains:<br>- 0.5 mg aluminium as $Al(OH)_3$<br>- 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

### *1.1. Steps taken for the assessment*

| | |
|---|---|
| Submission date: | 09/11/2016 |
| Start of procedure: | 28/11/2016 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 03/01/2017 |
| CHMP Rapporteur's updated assessment report circulated on: | 19/01/2017 |
| CHMP opinion: | 26/01/2017 |

## 2. Assessment of the post-authorisation measure PAM 091

The MAH submitted a report at Month 36 for Study 115411 (HPV-071 PRI), a Phase IIIb observer-blind, randomized, multicentre (Sweden, Hong Kong, France and Singapore) 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.

## 2.1.1. Clinical study

## 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*

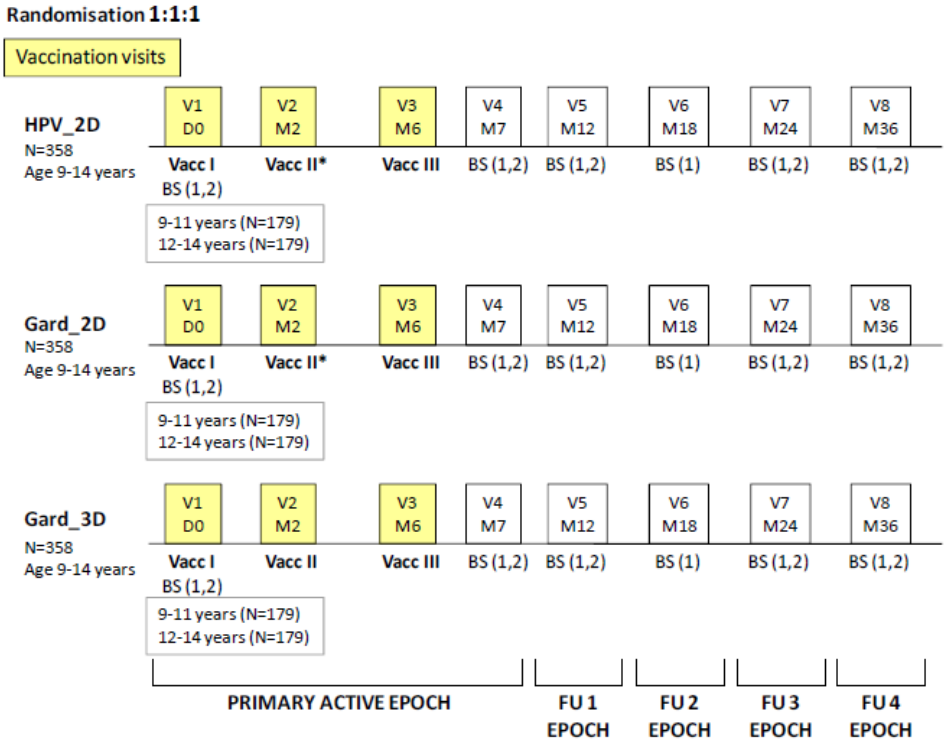
- If the primary non-inferiority objective is reached, the next objective is to evaluate sequentially if the immunogenicity (as determined by ELISA) of a **2-dose Cervarix** schedule is non-inferior/superior to that of a **2-dose Gardasil** schedule, both administered at 0, 6 months, at Months 12, 18, 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 compared to the 1036 subjects that completed the 36 months follow-up.

**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

**Table 3.** Number of subjects vaccinated, completed and withdrawn with reason for withdrawal up to Month 36 (Total vaccinated cohort).

| **Study population (Month 36 Total vaccinated cohort) –** | | | |
|---|---|---|---|
| **Number of subjects** | **HPV_2D** | **Gard_2D** | **Gard_3D** |
| Planned, N | 358 | 358 | 358 |
| Enrolled to Month 36, N (Month 36 Total Vaccinated cohort) | 351 | 339 | 346 |
| Completed to visit 8 M36, n (%) | 351 (100) | 339 (100) | 346 (100) |
| **Demographics** | **HPV_2D** | **Gard_2D** | **Gard_3D** |
| N (Month 36 Total Vaccinated cohort) | 351 | 339 | 346 |
| Females:Males | 351:0 | 339:0 | 346:0 |
| Mean Age, years (SD) | 14.5 (1.6) | 14.5 (1.6) | 14.6 (1.7) |
| Median Age, years (minimum, maximum) | 14 (11, 17) | 14 (11, 18) | 14 (11, 18) |
| Asian - East Asian Heritage, n (%) | 178 (50.7) | 175 (51.6) | 176 (50.9) |
| White - Caucasian / European Heritage, n (%) | 87 (24.8) | 79 (23.3) | 81 (23.4) |
| Asian - South East Asian Heritage, n (%) | 80 (22.8) | 73 (21.5) | 80 (23.1) |
| 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 | | | |

***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.

Table 3: Study population (at Month 36 TVC)

| **Study population (Month 36 Total vaccinated cohort) –** | | | |
|---|---|---|---|
| **Number of subjects** | **HPV_2D** | **Gard_2D** | **Gard_3D** |
| Planned, N | 358 | 358 | 358 |
| Enrolled to Month 36, N (Month 36 Total Vaccinated cohort) | 351 | 339 | 346 |
| Completed to visit 8 M36, n (%) | 351 (100) | 339 (100) | 346 (100) |
| **Demographics** | **HPV_2D** | **Gard_2D** | **Gard_3D** |
| N (Month 36 Total Vaccinated cohort) | 351 | 339 | 346 |
| Females:Males | 351:0 | 339:0 | 346:0 |
| Mean Age, years (SD) | 14.5 (1.6) | 14.5 (1.6) | 14.6 (1.7) |
| Median Age, years (minimum, maximum) | 14 (11, 17) | 14 (11, 18) | 14 (11, 18) |
| Asian - East Asian Heritage, n (%) | 178 (50.7) | 175 (51.6) | 176 (50.9) |
| White - Caucasian / European Heritage, n (%) | 87 (24.8) | 79 (23.3) | 81 (23.4) |
| Asian - South East Asian Heritage, n (%) | 80 (22.8) | 73 (21.5) | 80 (23.1) |
| 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 | | | |

## 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 4).

**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 2D, M36)***

The non-inferiority assessment of seroconversion rates is presented in **Error! Reference source not found.** and the non-inferiority assessment of anti-HPV-16 and anti-HPV-18 antibody GMT (ELISA) is presented in synopsis Table 1 to 3.

**Synopsis Table 1: Non-Inferiority assessment of anti HPV-16 seroconversion rates (HPV _2D vs Gard_2D) at Month 36 in initially seronegative subjects (Month 36 ATP cohort for immunogenicity)**

| | | | | | | Difference in seropositivity rate (Group 2 minus Group 1) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 95 % CI | |
| Group 1 | N | % | Group 2 | N | % | Difference | % | LL | UL |
| HPV_2D | 318 | 100 | Gard_2D | 306 | 99.3 | Gard_2D - HPV_2D | -0.65 | -2.35 | 0.55 |

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 anti-HPV-16 antibody titre ≥ 19 EU/ml; 95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit

**Synopsis Table 2: Non-Inferiority assessment of anti HPV-18 seroconversion rates (HPV _2D vs Gard_2D) at Month 36 in initially seronegative subjects (Month 36 ATP cohort for immunogenicity)**

| | | | | | | Difference in seropositivity rate (Group 2 minus Group 1) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 95 % CI | |
| Group 1 | N | % | Group 2 | N | % | Difference | % | LL | UL |
| HPV_2D | 322 | 100 | Gard_2D | 310 | 86.1 | Gard_2D - HPV_2D | -13.87 | -18.17 | -10.46 |

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 anti-HPV-18 antibody titre ≥ 18 EU/ml; 95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit

**Synopsis Table 3: Non-inferiority assessment of anti HPV-16 and HPV-18 immune response for (HPV _2D vs Gard_2D) at Month 36 in initially seronegative subjects (Month 36 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 antibody (EU/ml) | 306 | 379.8 | 318 | 1061.4 | 0.36 | 0.31 | 0.42 |
| anti-HPV-18 antibody (EU/ml) | 310 | 71.0 | 322 | 486.5 | 0.15 | 0.12 | 0.17 |

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

At the Month 36 time point:

**Non-inferiority in terms of both seroconversion and GMT ratio was met** since:

- the upper limit of the 95% CI for the difference in seroconversion rates (HPV-6/11/16/18 (0, 6) schedule minus HPV-16/18 (0, 6) schedule) for both anti-HPV-16 and anti-HPV-18 antibodies was below 5% in the Month 36 ATP cohort for immunogenicity.
- the upper limit of the 95% CI for the GMT ratio (HPV-6/11/16/18 (0, 6) schedule divided by HPV-16/18 (0, 6) schedule) for both anti-HPV-16 and anti-HPV-18 antibodies was below 2 in the Month 36 ATP cohort for immunogenicity.

***Superiority analysis on primary objective (Cervarix 2-dose vs Gardasil 2-dose, M36)***

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.

| Synopsis Table 4: Superiority assessment of anti HPV-18 immune response for (HPV _2D vs Gard_2D) at Month 36 regardless of the serostatus (Month 36 Total Vaccinated cohort) | | | | | | |
|---|---|---|---|---|---|---|
| | | | | GMT ratio (HPV_2D / Gard_2D) | | |
| HPV_2D | | Gard_2D | | | 95% CI | |
| N | GMT | N | GMT | Value | LL | UL |
| 349 | 479.7 | 339 | 70.1 | 6.84 | 5.81 | 8.05 |
| 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 Number of subjects with pre-vaccination results available | | | | | | |

| Synopsis Table 5: Superiority assessment of anti HPV-16 immune response for (HPV _2D vs Gard_2D) at Month 36 regardless of the serostatus (Month 36 Total Vaccinated cohort) | | | | | | |
|---|---|---|---|---|---|---|
| | | | | GMT ratio (HPV_2D / Gard_2D) | | |
| HPV_2D | | Gard_2D | | | 95% CI | |
| N | GMT | N | GMT | Value | LL | UL |
| 349 | 1033.0 | 339 | 372.1 | 2.78 | 2.38 | 3.24 |
| 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 Number of subjects with pre-vaccination results available | | | | | | |

At the Month 36 time point:

**Superiority in terms of GMT ratio was met** as:

- the lower limit of the 95% CI for the GMT ratio (HPV-16/18 (0, 6) schedule divided by HPV-6/11/16/18 (0, 6) schedule) for both anti-HPV-18 and anti-HPV-16 antibodies was above 1, in the Month 36 Total Vaccinated cohort.

***Assessor'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 36.

- 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 2D vs Gardasil 3D, M36)***

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 36, was also met for this study.

**Synopsis Table 6: Non-Inferiority assessment of anti HPV-16 seroconversion rates (HPV _2D vs Gard_3D) at Month 36 in initially seronegative subjects (Month 36 ATP cohort for immunogenicity)**

| | | | | | | Difference in seropositivity rate (Group 2 minus Group 1) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 95 % CI | |
| **Group 1** | **N** | **%** | **Group 2** | **N** | **%** | **Difference** | **%** | **LL** | **UL** |
| HPV_2D | 318 | 100 | Gard_3D | 309 | 99.7 | Gard_3D - HPV_2D | -0.32 | -1.81 | 0.87 |

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

**Synopsis Table 7: Non-inferiority assessment of anti HPV-18 seroconversion rates (HPV _2D vs Gard_3D) at Month 36 in initially seronegative subjects (Month 36 ATP cohort for immunogenicity)**

| | | | | | | Difference in seropositivity rate (Group 2 minus Group 1) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 95 % CI | |
| **Group 1** | **N** | **%** | **Group 2** | **N** | **%** | **Difference** | **%** | **LL** | **UL** |
| HPV_2D | 322 | 100 | Gard_3D | 320 | 92.8 | Gard_3D - HPV_2D | -7.19 | -10.56 | -4.84 |

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

**Synopsis Table 8: Non-inferiority assessment of anti HPV-16 and HPV-18 immune response for (HPV _2D vs Gard_3D) at Month 36 in initially seronegative subjects (Month 36 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 antibody (EU/ml) | 309 | 472.4 | 318 | 1061.4 | 0.45 | 0.39 | 0.51 |
| anti-HPV-18 antibody (EU/ml) | 320 | 119.1 | 322 | 486.5 | 0.24 | 0.21 | 0.29 |

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

At the Month 36 time point:

**Non-inferiority in terms of both seroconversion and GMT ratio was met** since:

- the upper limit of the 95% CI for the difference in seroconversion rates (HPV-6/11/16/18 [0, 2, 6] schedule minus HPV-16/18 [0, 6] schedule for both anti-HPV-16 and anti-HPV-18 antibodies was below 5% in the Month 36 ATP cohort for immunogenicity.
- the upper limit of the 95% CI for the GMT ratio (HPV-6/11/16/18 [0, 2, 6] schedule divided by HPV-16/18 [0, 6] schedule) for both anti-HPV-16 and anti-HPV-18 antibodies was below 2 in the Month 36 ATP cohort for immunogenicity

***Superiority analysis on secondary objective (Cervarix 2D vs Gardasil 3D, M36)***

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.

| Synopsis Table 9: Superiority assessment of anti HPV-18 immune response for (HPV _2D vs Gard_3D) at Month 36 regardless of the serostatus (Month 36 Total Vaccinated cohort) | | | | | | |
|---|---|---|---|---|---|---|
| | | | | GMT ratio (HPV_2D / Gard_3D) | | |
| HPV_2D | | Gard_3D | | | 95% CI | |
| N | GMT | N | GMT | Value | LL | UL |
| 349 | 479.7 | 346 | 115.9 | 4.14 | 3.49 | 4.91 |
| 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 | | | | | | |

| Synopsis Table 10: Superiority assessment of anti HPV-16 immune response for (HPV _2D vs Gard_3D) at Month 36 regardless of the serostatus (Month 36 Total Vaccinated cohort) | | | | | | |
|---|---|---|---|---|---|---|
| | | | | GMT ratio (HPV_2D / Gard_3D) | | |
| HPV_2D | | Gard_3D | | | 95% CI | |
| N | GMT | N | GMT | Value | LL | UL |
| 349 | 1033.0 | 346 | 449.6 | 2.30 | 2.00 | 2.64 |
| 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 | | | | | | |

At the Month 36 time point:

**Superiority in terms of GMT ratio was met** as:

- the lower limit of the 95% CI for the GMT ratio (HPV-16/18 [0,6] schedule divided by HPV-6/11/16/18 [0, 2, 6] schedule) for both anti-HPV-18 and anti-HPV-16 antibodies was above 1, in the Month 36 Total Vaccinated cohort.

**Assessor'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 36**

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

In the Month 36 ATP cohort for immunogenicity, all initially seronegative subjects in the HPV_2D group, and at least 99.3% of subjects in the Gard_2D and Gard_3D groups had seroconverted for anti-HPV-16 antibodies when measured by ELISA. All initially seronegative subjects in the HPV_2D group, and at least 86.1% of subjects in the Gard_2D and Gard_3D groups had seroconverted for anti-HPV-18 antibodies, when measured by ELISA.

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

GMT levels for neutralising antibodies against both HPV-16 and HPV-18, which had reached a peak response at Month 7, showed a further decline at Month 36 in all three groups. This is in line with previous observations.

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

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.

- In the month 24 ATP cohort for immunogenicity, all initially seronegative subjects in HPV_2D and Gard_2D groups, and 98.9% of subjects in the 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, 90.4% of subjects and in Gard_3D group, 96.7% of subjects had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA at M24.
  - 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 24 in all three groups.

***Anti-HPV-16/18 neutralising antibodies measured by PBNA at Month 36***

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 but well at M36. In the Month 36 ATP cohort for immunogenicity, all initially seronegative subjects in the HPV_2D, Gard_2D Gard_3D groups had seroconverted for anti-HPV-16 neutralising antibodies when measured by PBNA. All initially seronegative subjects in HPV_2D group, 86.2% of subjects in Gard_2D group and 94.5% of subjects in Gard_3D group had seroconverted for anti-HPV-18 neutralising antibodies when measured by PBNA.

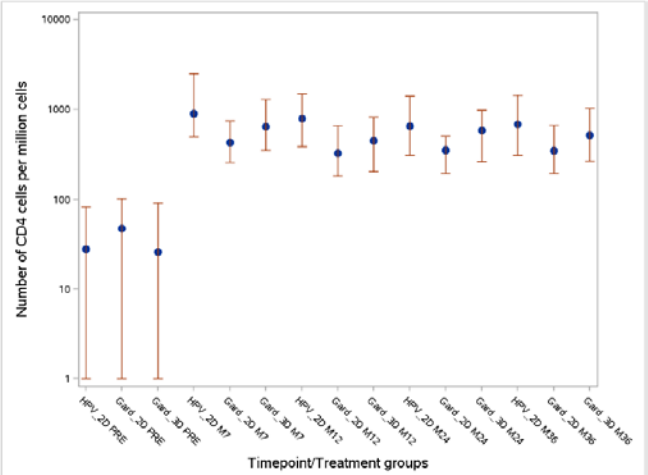
GMT levels for neutralising antibodies against both HPV-16 and HPV-18, which had reached a peak response at Month 7, showed a further decline at Month 36 in all three groups.

***T-cell-mediated immune responses***

- **CD4+ T cell response**

At Month 36, overall CD4+ T cell response (in terms of median frequency of HPV-16/18 antigenspecific CD4+ T cells per million CD4+ T cells expressing at least two different immune markers [all doubles]) was1012.0, 685.0 and 842.5 cells per million CD4+ T cells in HPV_2D, Gard_2D and Gard_3D groups, respectively for HPV-16. HPV-18 specific CD4+ T cell response was 682.0, 350.0 and 516.0 cells per million CD4+ T cells in HPV_2D, Gard_2D and Gard_3D groups, respectively. **Figure 4.** CD4+ all doubles response by intracellular cytokine staining to HPV-16/18 (Month 36 ATP cohort for immunogenicity)

**HPV-16** **HPV-18**




- **CD8+ T cell response**

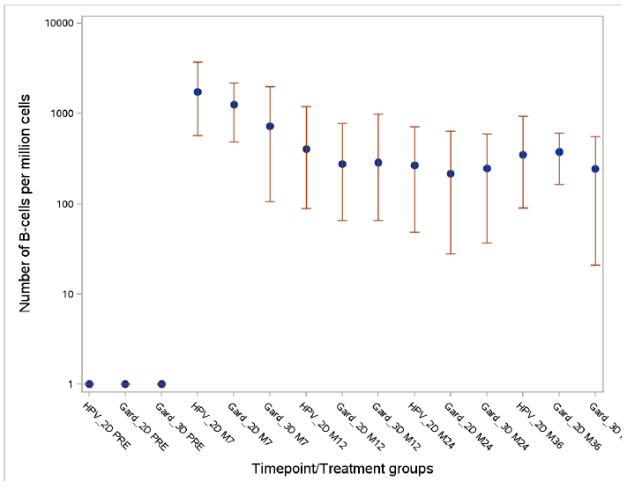
As observed in the previous time points, HPV-16 and HPV-18 specific CD8+ T cells response was undetectable (up to 4.0 cells per million CD8+ T cells) in all three groups at Month 36.

***Memory B-cell-mediated immune responses***

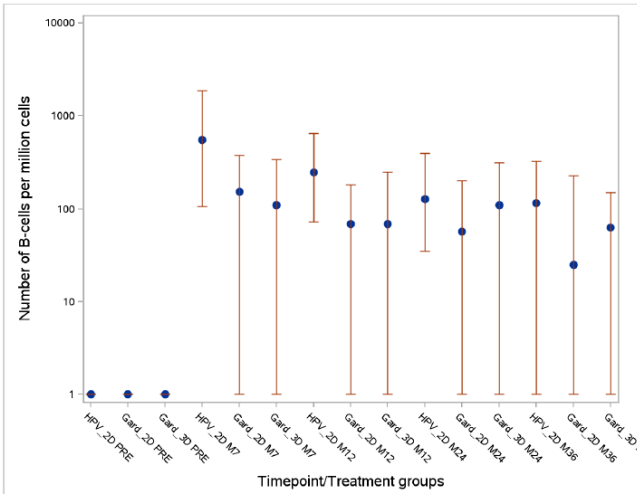
At Month 36, B cell response (in terms of median frequency of HPV-16/18 antigen-specific memory B cells per million memory B cells in subjects with detectable B cells) was 353.0, 390.0 and 246.0 cells per million memory B cells in HPV_2D, Gard_2D and Gard_3D groups, respectively, for HPV-16. The HPV-18 specific memory B cell response was 116.0 cells, 25.0 and 69.5 cells per million memory B cells in HPV_2D, Gard_2D and Gard_3D groups, respectively.

**Figure 5.** B-cell elispot response to HPV-16/18 (Month 36 ATP cohort for immunogenicity)

**HPV-16**




**HPV-18**




## *Safety results*

The primary analysis of safety is based on the TVC.

***Serious adverse events:***

- A SAE with a fatal outcome due to committed suicide was reported for subject (Gard_3D group) at Month 36. The investigator considered that there was no causal relationship between the subject's suicide and the vaccine administered.
- Up to the end of the study (Month 36), a total of 46 subjects (21 subjects in the HPV_2D group, 11 subjects in the Gard_2D group and 14 subjects in the Gard_3D group) reported at least one SAE. None of the 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 (food dependant exercise induced anaphylaxis), tension headache and juvenile idiopathic arthritis which were ongoing at the time of the data lock point of this study for the Month 36 time point.

***Medically significant conditions:***

- Up to Month 36, a total of 219 subjects reported at least one MSC (77 subjects in HPV_2D group,79 subjects in Gard_2D group and 63 subjects in Gard_3D group) in the TVC.

***Potential Immune-Mediated Dissorders (pIMDs) up to Month 12:***

- A total of six subjects in the TVC (three subjects each in the HPV_2D and Gard_2D groups) reported at least one pIMD up to Month 12. **One pIMD (arthritis reactive) was considered by the investigator to have a possible causal relationship to vaccination.**

***Withdrawals due to adverse events /serious adverse events:***

- Subject (Gard_3D group) was withdrawn as a result of a fatal SAE (completed suicide). There were no other withdrawals due to adverse events or serious adverse events from Month 24 to Month 36.

***Concomitant medications /vaccinations:***

- Up to Month 36, in the Total Vaccinated cohort, any concomitant medication was received by 47.6%, 43.9% and 45.0% of subjects in HPV_2D, Gard_2D and Gard_3D groups, respectively. Any antipyretic medication was received by 30.6%, 28.5% and 26.5% of subjects in HPV_2D, Gard_2D and Gard_3D groups, respectively. Prophylactic antipyretic medication was received by 1.4%, 0.6% and 0.6% of subjects in HPV_2D, Gard_2D and Gard_3D groups, respectively. Any antibiotic medication was received by 13.4%, 11.7% and 14.0% of subjects in HPV_2D, Gard_2D and Gard_3D groups, respectively.

***Pregnancies:***

- There was one report of a pregnancy (Gard_3D group) up to Month 36, which was electively terminated with no apparent congenital anomaly.

More SAEs were reported for Cervarix over the entire study period up until Month 36, as well as in the period between Month 18 and Month 24, but not between M24 and M36 as shown in Tables 8 and 9 below.

**Table 8.** Global Summary of SAEs from Month 0 - Month 36 (Month 36 Total Vaccinated cohort)

| | Group | | | |
|---|---|---|---|---|
| | HPV_2D | Gard_2D | Gard_3D | Total |
| Number of subjects with at least one SAE reported | 21 | 11 | 14 | 46 |
| Number of doses followed by at least one SAE | 21 | 11 | 14 | 46 |
| Number of SAEs classified by MedDRA Preferred Term* | 24 | 13 | 17 | 54 |
| Number of SAEs reported** | 24 | 13 | 17 | 54 |

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

**Table 9.** Global Summary of SAEs from Month 24 – Month 36 (Month 24 Total Vaccinated cohort)

| | Group | | | |
|---|---|---|---|---|
| | HPV_2D | Gard_2D | Gard_3D | Total |
| Number of subjects with at least one SAE reported | 3 | 5 | 7 | 15 |
| Number of doses followed by at least one SAE | 3 | 5 | 7 | 15 |
| Number of SAEs classified by MedDRA Preferred Term* | 3 | 7 | 8 | 18 |
| Number of SAEs reported** | 3 | 7 | 8 | 18 |

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

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.

## 2.1.2. Discussion on clinical aspects

### *Immunogenicity results*

Non-inferiority and superiority of immune responses to both HPV-16 and HPV-18 antigens was demonstrated at Month 36 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.

### *Safety results*

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 36 regardless of the number of Gardasil doses.

Up to the end of the study (Month 36), a total of 46 subjects (21 subjects in the HPV_2D group, 11 subjects in the Gard_2D group and 14 subjects in the Gard_3D group) reported at least one SAE. The occurrence of the SAEs after Cervarix were reported the first 18 months. According to the CSR, none of the SAEs were considered by the investigator to have a possible causal relationship to vaccination.

# 3. Rapporteur's overall conclusion

In conclusion, non-inferiority and superiority of immune responses to both HPV-16 and HPV-18 antigens was demonstrated up to Month 36 by the Applicant when HPV-16/18 vaccine was administered according to a 2-dose schedule at 0,6 months in 9-14 year old females versus Merck's HPV-6/11/16/18 L1 VLP recombinant vaccine administered according to a 2-dose schedule at 0, 6 months or according to a 3-dose schedule at 0,2,6 months.

The safety profile of HPV-16/18 vaccine was in line with the known safety profile of the vaccine, and that of HPV-6/11/16/18 vaccine was in line with the Prescribing Information. Both vaccines were generally well tolerated when administered according to a 3-dose or 2-dose schedule in subjects aged 9-14 years.

The HPV-071 PRI study results are in line with the approved PI. No changes to the SmPC are needed. 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.