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EMA/632894/2012
Committee for Medicinal Products for Human Use (CHMP)

Cervarix

(human papillomavirus1 type 16 L1 protein / human papillomavirus type 18 L1 protein)

Procedure No. EMEA/H/C/000721/P45/045

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

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

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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1. Recommendation

The conclusions of the MAH are endorsed: this clinical trial does not change the positive risk/benefit analysis of Cervarix. No changes are proposed to the SPC.

2. Introduction

Cervarix is indicated for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

The MAH submitted one completed paediatric study for Cervarix, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Cervarix and that there is no consequential regulatory action.

3. Scientific discussion

3.1. Information on the pharmaceutical formulation used in the clinical studies

Cervarix suspension for injection. Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed), 0.5 ml dose

3.2. Non-clinical aspects

Not applicable.

3.3. Clinical aspects

3.3.1. Introduction

The MAH submitted a report and extended synopsis for study: 104951 (HPV-033), a phase III, double-blind, randomised, controlled study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in healthy female subjects aged 10 -14 years.

3.3.2. Clinical studies

Clinical study 104951 (HPV-033)

Description

This study is a double-blind, randomised, controlled study involving 321 healthy female subjects between 10 and 14 years of age with as aim to evaluate the immunogenicity and safety of GSK's HPV-16/18 vaccine administered intramuscularly according to a 0, 1, 6 month schedule. This was evaluated in comparison with the control group, receiving the HAV-vaccine at the same time schedule.

Methods

- Objectives

  The **primary** objective was to evaluate antibody responses against HPV-16 and HPV-18 (by enzyme-linked immunosorbent assay [ELISA]) in all HPV-16/18 L1 VLP AS04 vaccine recipients at Month 7.

  The **secondary** objectives were to evaluate:

  – Serious adverse events (SAEs) up to Month 7

  – Solicitated local and general symptoms (Days 0 – 6)

  – Unsolicited symptoms (Days 0 – 29)

  – Biochemical and haematological parameters at Months 0 and 7

  – Occurrence of new onset chronic diseases and other medically significant conditions

- Study design

  A phase III, multicentre, double-blind, randomised and controlled trial with two parallel groups, HPV and HAV (Hepatitis A Virus) vaccine groups. All subjects received either the candidate HPV-16/18 L1 VLP S04 vaccine or the HAV control vaccine according to a 0, 1, 6 month schedule. Four study visits were scheduled at Months 0, 1, 6 and 7. Blood samples were drawn from all subjects at two time points in the study: one prior to vaccination and the second blood sample was drawn one month after the third vaccine dose (i.e. post-dose 3 Month 7).

- Study population /Sample size

  321 healthy female subjects between 10 and 14 years of age.

- Treatments

  Study vaccine (**HPV**): three doses of HPV-16/18 L1 VLP AS04 vaccine administered by intramuscular injection in the non-dominant arm.

  Reference vaccine (**HAV**): three doses of GSK Biologicals' hepatitis A vaccine (Havrix) administered by intramuscular injection in the non-dominant arm.

- Criteria for evaluation

Primary endpoint - **immunogenicity:** Seroconversion rates to HPV-16 and HPV-18 as assessed by enzyme-linked immunosorbent assay (ELISA) at Month 7

Secondary endpoints - **safety:**

- Occurrence of SAEs up to Month 7
- Occurrence, intensity and relationship to vaccination of general symptoms, and local symptoms during the first 7 days
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 after any vaccination.
- Occurrence of clinically relevant abnormalities in biochemical and haematological parameters at Months 0 and 7
- Occurrence of new onset chronic diseases and other medically significant conditions throughout the study period (up to Month 7) regardless of causal relationship to vaccination and intensity.
- Anti-HPV-16/18 antibody titers (by ELISA) at Month 0 and Month 7.

- Statistical method

  Analysis of **demography**: Demographic characteristics (age, race) of each study cohort were tabulated. The mean age (plus range and standard deviation) of the enrolled subjects, as a whole and per group, were calculated. The distribution of subjects enrolled among the study centers were tabulated as a whole and per group.

  Analysis of **immunogenicity**: For each time point that serological results were available, the following were calculated with their exact 95% confidence intervals for each group: Anti-HPV-16, anti-HPV-18 and anti-HAV (all measured by ELISA): seropositivity and seroconversion rates for the antibodies. Geometric mean titers (GMTs) and range of antibody titers were tabulated for antibodies against each antigen. The distribution of antibody titers at Month 7 for each antigen for subjects who were initially seronegative at pre-vaccination was displayed using Reverse cumulative distribution curves (RCCs).

  Analysis of **safety**: The two-sided standardized asymptotic 95% CI for the difference of SAE rates (SAE rate in HAV Group minus SAE rate in HPV control Group) was computed (Proc StatXact 5.0). The comparison was done by subject, considering all SAEs at the same and then considering individual SAEs classified by the Medical Dictionary for Regulatory Activities (MedDRA). Proc StatXact 5.0 was used to calculate the exact 95% CIs for proportion within a group assuming independence between doses and to derive the standardized asymptotic 95% CI for the group difference in proportion. The percentage of subjects with at least one solicit /one solicit and one unsolicited local adverse event (AE), with at least one solicited/unsolicit general AE and with any AE reported during the 7-day solicited follow-up period was tabulated after each vaccine dose and overall. The proportion of subjects with at least one new onset chronic disease (NOCD), the proportion of subjects with at least one report of unsolicited AE and the haematology and biochemistry analysis with the percentage of subjects outside the normal ranges were tabulated.

Results

- Number analyzed/ Recruitment

Demography results: The mean age of the subjects in the ATP cohort for immunogenicity was 11.9 years with a standard deviation (SD) of 1.39 years. The population was predominantly of South East Asian Heritage (77%) and 23% of subjects were of East Asian Heritage. The demographic profiles were similar for both groups (HPV and HAV) with respect to mean age and racial distribution.

Number of subjects:	HPV Group	HAV Group	Total
Planned	150	150	300
Enrolled & vaccinated (=Total vaccinated cohort)	160	161	321
Completed	158	161	319
According-to-protocol (ATP) cohort for safety:	126	132	258
ATP cohort for immunogenicity:	120	128	248

- Immunogenicity results

Immunogenicity analyses were performed on the ATP cohort (primary analysis) and on the Total vaccinated cohort. The immunogenicity data obtained from both analyses were consistent. Seroconversion/ seropositivity rates and GMTs for anti-HPV-16, anti-HPV-18 and anti-HAV antibodies by pre-vaccination status for the ATP cohort for immunogenicity are presented in the table below.

Table 1: Seroconversion rates/seropositivity rates and GMTs for anti-HPC-16, anti-HPV-18 and anti-HAV antibodies by pre-vaccination status (ATP cohort for immunogenicity)

Group	Pre-vacc Status	Timing	N		95% CI		GMT	95% CI		Min.	Max.
				%	LL	UL	(El.U/mL)	LL	UL		
Anti-HPV-16 antibodies (≥ 8 El.U/mL)											
HPV	S-	PRE	112	0.0	0.0	3.2	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	112	100	96.8	100	19619.8	17188.6	22394.8	4215.0	83057.0
	S+	PRE	7	100	59.0	100	24.7	15.1	40.1	10.0	40.0
		PIII(M7)	7	100	59.0	100	20778.6	13383.8	32259.2	9978.0	37427.0
	Total	PRE	119	5.9	2.4	11.7	4.5	4.1	4.8	<8.0	40.0
		PIII(M7)	119	100	96.9	100	19686.1	17356.8	22328.1	4215.0	83057.0
HAV	S-	PRE	120	0.0	0.0	3.0	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	120	6.7	2.9	12.7	4.8	4.2	5.5	<8.0	590.0
	S+	PRE	8	100	63.1	100	27.4	11.0	68.1	9.0	142.0
		PIII(M7)	8	75.0	34.9	96.8	34.4	3.7	316.5	<8.0	15391.0
	Total	PRE	128	6.3	2.7	11.9	4.5	4.1	5.0	<8.0	142.0
		PIII(M7)	128	10.9	6.1	17.7	5.4	4.5	6.6	<8.0	15391.0

Gro-up	Pre-vacc Status	Timing	N	%	95% CI LL	GMT UL	GMT (EI.U/mL)	95% CI LL	95% CI UL	Min.	Max.
Anti-HPV-18 antibodies (≥ 7 EI.U/mL)											
HPV	S-	PRE	115	0.0	0.0	3.2	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	115	100	96.8	100	9894.5	8674.1	11286.6	1765.0	121564.0
	S+	PRE	5	100	47.8	100	10.8	6.7	17.5	8.0	21.0
		PIII(M7)	5	100	47.8	100	9097.1	6155.6	13444.0	5522.0	11677.0
	Total	PRE	120	4.2	1.4	9.5	3.7	3.5	3.8	<7.0	21.0
		PIII(M7)	120	100	97.0	100	9859.9	8687.9	11189.9	1765.0	121564.0
HAV	S-	PRE	119	0.0	0.0	3.1	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	119	7.6	3.5	13.9	4.7	3.8	5.9	<7.0	13868.0
	S+	PRE	9	100	66.4	100	19.5	11.1	34.0	8.0	81.0
		PIII(M7)	9	66.7	29.9	92.5	10.1	4.4	23.6	<7.0	83.0
	Total	PRE	128	7.0	3.3	12.9	3.9	3.6	4.3	<7.0	81.0
		PIII(M7)	128	11.7	6.7	18.6	5.0	4.0	6.1	<7.0	13868.0
Anti-HAV antibodies (≥ 15 mIU/mL)											
HPV	S-	PRE	105	0.0	0.0	3.5	7.5	7.5	7.5	<15.0	<15.0
		PIII(M7)	105	10.5	5.3	18.0	8.9	7.9	10.1	<15.0	647.0
	S+	PRE	15	100	78.2	100	46.5	26.1	82.9	17.0	497.0
		PIII(M7)	15	73.3	44.9	92.2	84.9	28.2	255.5	<15.0	2730.0
	Total	PRE	120	12.5	7.2	19.8	9.4	8.3	10.7	<15.0	497.0
		PIII(M7)	120	18.3	11.9	26.4	11.8	9.6	14.6	<15.0	2730.0
HAV	S-	PRE	115	0.0	0.0	3.2	7.5	7.5	7.5	<15.0	<15.0
		PIII(M7)	115	100	96.8	100	1828.0	1557.6	2145.3	16.0	14783.0
	S+	PRE	13	100	75.3	100	69.4	18.5	259.8	15.0	18908.0
		PIII(M7)	13	100	75.3	100	3363.6	1801.6	6279.6	740.0	29180.0
	Total	PRE	128	10.2	5.5	16.7	9.4	8.0	11.1	<15.0	18908.0
		PIII(M7)	128	100	97.2	100	1944.8	1661.7	2276.1	16.0	29180.0

- **Anti-HPV-16 and anti-HPV-18 antibodies**: At post-dose 3 in the HPV Group, 100% seroconversion rates were observed for anti-HPV-16 antibodies and anti-HPV-18 antibodies in initially seronegative subjects, GMTs were high for the anti-HPV-16 antibodies (19619.8 EI.U/mL; 95% CI: 17188.6; 22394.8) and anti-HPV-18 antibodies (9894.5 EI.U/mL; 95% CI: 8674.1; 11286.6) at the post-dose 3 time point. Initially seropositive subjects for HPV-16 and/or HPV-18 antigens also demonstrated 100% seropositivity rates one month after the third dose of the HPV vaccine, and achieved GMTs that were similar to those subjects who were initially seronegative (20778.6 EI.U/mL; 95% CI: 13383.8; 32259.2).
- **Anti-HAV antibodies**: One month after the third dose of the HAV vaccine, 100% seroconversion rates were observed for anti-HAV antibodies in initially seronegative subjects. The GMTs for these subjects were 1828.0 mIU/mL (95% CI: 1557.6; 2145.3). In subjects who were initially seropositive for anti- HAV, 100% seropositivity rates were observed with GMTs of 3363.6 mIU/mL (95% CI: 1801.6; 6279.6).

- Effectiveness results

  No effectiveness research was performed.

- Safety results

  Any symptom (**solicited / unsolicited**): During the 30-day post-vaccination period, the incidence of any symptom (solicited and unsolicited) tended to be higher in the HPV Group (after 70.7% of doses) than in the HAV Group (after 48% of doses). This was due to the higher incidence of local symptoms in the HPV Group (after 65% of doses) than in the HAV Group (after 32.1% of doses). Grade 3 symptoms (solicited and unsolicited) were reported after 2.7% of doses in the HPV Group and after 0.8% of doses in the HAV Group. Reporting of solicited and unsolicited symptoms assessed by the investigator as related to vaccination followed a similar pattern (i.e. higher incidence in the HPV Group than in the HAV Group).

The most frequent solicited **local symptom** was pain, after 60.3% HPV doses and 30.4% HAV doses. Regarding solicited general symptoms: The general pattern of AE's were similar for both groups except Myalgia. Myalgia was reported more frequently in the HPV Group (after 16.7% of doses) than in the HAV Group (after 8.3% of doses), and related to the vaccine respectively after 9.3% and 3.9%. Other mentioned were headache and fatigue. **Unsolicited symptoms** reported during the 30-day post-vaccination period were similar in incidence, intensity and relationship to vaccination between the two groups. Five subjects (3 in the HPV Group and 2 in the HAV Group) reported 5 AEs classified as **NOCD**s (new onset of chronic diseases) according to GSK assessment. In both groups, the **biochemical and haematological parameters** of most of the subjects were within the normal ranges One subject reported an SAE: an acute gastroenteritis approximately five months after receiving the second dose of HAV vaccine with diarrhoea and abdominal pain after a school meal. The event resolved after duration of 10 days and the SAE was assessed by the investigator to have no causal relationship to the vaccination. The subject received the third vaccine dose and there were no further reports of adverse events. There were no withdrawals due to AEs in this study.

4. Conclusion

One month after the third vaccine dose, 100% of subjects who were seronegative at pre-vaccination had seroconverted for both HPV-16 and HPV-18 antigens with high GMTs. A similar immune response was also elicited in subjects who were seropositive at pre-vaccination.

All subjects who were initially seronegative in the HAV Group had seroconverted for anti-HAV antibodies at the post-dose 3 time point.

There were no differences observed in adverse event patterns (with respect to the relative frequency of different events, duration, relative intensity and reported relationship to vaccination) between groups. However, the overall safety profile tended to be higher in the HPV Group than in the HAV Group for all the local symptoms. For the general symptoms, the incidence of **Myalgia** was about 2-fold higher in the HPV Group than in the HAV Group, however, there were no reports of Myalgia of grade 3 intensity in either group. The incidence of solicited symptoms generally did not increase with the number of doses.

Unsolicited symptoms reported within the 30-day post-vaccination period were similar in incidence, intensity and relationship to vaccination between the two groups.

No differences in incidence rates were identified between groups for any unsolicited symptom classified by either the Preferred Term or Primary System Organ Class.

The incidence and pattern of NOCDs and medically significant conditions were similar in both groups.

Vaccination did not affect the biochemical and haematological parameters in both groups.

The reactogenicity results observed for the subset of subjects who received a vaccine that might have been exposed to a deviated temperature was similar to those in the other subjects.

The immunogenicity results observed for the subset of subjects who received a vaccine that might have been exposed to a deviated temperature was similar to those in the other subjects.

Clinical expert statement

GlaxoSmithKline has reviewed the results of this study and has concluded that they have no impact on the approved SPS of Cervarix.

Rapporteur's conclusion study 104951

The conclusions of the MAH are endorsed although the effectiveness was not assessed in this study; the safety profile of the vaccine seemed to be as expected. The efficacy and safety of the vaccine tested in this clinical trial seems to be acceptable. The conclusion of the clinical expert of the MAH can also be endorsed; no changes the existing SPC are needed.