25 June 2015
EMA/527704/2015
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/P46/086

Note

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

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1. Introduction

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

Study HPV-070 was a Phase IIIb open-label, randomised, multi-centre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine when administered intramuscularly according to alternative 2-dose schedules in 9 - 14 year old healthy females compared to the standard 3-dose schedule for GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in 15 - 25 year old healthy females, the age group where vaccine efficacy was demonstrtaed. The study was planned for 3 years and has completed.

The current report presents the results of Study HPV-070 up to month 18. The study reports HPV-070 Month 24 & 36 will be merged together due to the availability of both data at the same time following delay in availability of certain laboratory results and submitted at the same time.

1.1. Steps taken for the assessment

Submission date:	26/03/2015
Start of procedure:	26/04/2015
CHMP Rapporteur's preliminary assessment report circulated on:	26/05/2015
CHMP Comments	10/06/2015
CHMP opinion:	25/06/2015

2. Assessment of the post-authorisation measure PAM

The study was conducted in 1,447 healthy females aged 9-25 years.

Study design: A Phase IIIb, open-label, randomized, multi-centre study with 3 parallel groups.

Blood samples for antibody determination:

- For group (0,6) and group (0,1,6), blood samples were drawn at Day 0, Month 7, Month 12, and Month 18 and will be drawn from these two groups at Month 24 and Month 36.
- For group (0,12), blood samples were drawn at Day 0, Month 13 and Month 18 and will be drawn from this group at Month 24 and Month 36.

Primary Objective :

> *To demonstrate that the immunogenicity (as determined by ELISA) of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered according to a 2-dose schedule of 0,6 months in 9-14 year old females is non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females, 1 month after the last dose of study vaccine.*

Secondary Objective

- To demonstrate that the immunogenicity (as determined by ELISA) of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered according to a 2-dose schedule of 0,6 months in 9-14 year old females is non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females, 6 months, 12 months, 18 months and 30 months after the last dose of study vaccine.
- To evaluate if the immunogenicity (as determined by ELISA) of GSK Biologicals' HPV-16/18 L1

VLP AS04 vaccine administered according to a 2-dose schedule of 0,12 months in 9-14 year old females is non-inferior to that administered according to a 2-dose schedule of 0,6 months in 9-14 year old females, [1 month], 6 months and 12 months after the last dose of study vaccine.

- To assess the immune responses to HPV types 16 and 18 (as determined by ELISA) at [Day 0] and [Months 7], [12], 18, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at [Day 0] and [Months 13], 18, 24 and 36 (for subjects having received their last vaccine dose at Month 12) in all subjects.
- To assess the immune responses to HPV types 16 and 18 (as determined by PBNA) at [Day 0] and [Months 7], [12], 18, 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at [Day 0] and [Months 13], 18, 24 and 36 (for subjects having received their last vaccine dose at Month 12) in a subset of subjects.
- To assess the T cell-mediated and memory B cell immune responses specific to HPV types 16 and 18 at [Day 0] and [Months 7], [12], 24 and 36 (for subjects having received their last vaccine dose at Month 6) or at [Day 0] and [Months 13], 18 and 36 (for subjects having received their last vaccine dose at Month 12) in a sub-cohort of subjects.

MAH's Conclusions:

The primary objective was already evaluated at the primary active epoch phase of the study.

The analysis of immunogenicity was based on the Month 18 ATP cohort. A second analysis based on

the Month 18 TVC was performed to complement the ATP analysis.

- The secondary objectives of non-inferiority for this study were met since:
    - the upper limit of the 95% CI for the differences in seroconversion rates (Group 0,1,6 minus Group 0,6; Group 0,1,6 minus Group 0,12 and Group 0,6 minus Group 0,12) for both anti- HPV-16 and anti-HPV-18 antibodies were below 5% at Month 18 in the ATP cohort for immunogenicity.
    - the upper limit of the 95% CI for the GMT ratio (Group 0,1,6 divided by Group 0,6; Group 0,1,6 divided by Group 0,12 and Group 0,6 divided by Group 0,12) was below 2 at Month 18 in the ATP cohort for immunogenicity.

- At Month 18 in the groups (0,6), (0,1,6) and (0,12), all initially seronegative subjects remained seroconverted for antibodies against HPV-16 and all initially seronegative subjects [except one subject in group (0,6)] remained seroconverted for antibodies against HPV-18 as measured by ELISA.

- The kinetics of antibodies measured by ELISA against both HPV-16 and HPV-18 in the groups (0,6) and (0,1,6) followed a similar pattern, i.e. after a peak response at Month 7, a decline in antibody titres was observed at Month 18.

- All initially seronegative subjects in group (0,6), group (0,1,6) and group (0,12) had seroconverted for both anti-HPV-16 and anti-HPV-18 neutralising antibodies when measured by PBNA at Month 18.

- Overall, the CD4+ T cell responses against HPV-16/18 (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 follows:
    - HPV-16 specific CD4+ T cell response was 101.0 cells per million CD4+ T cells in group (0,12) at pre time point and 1905.5 cells per million CD4+ T cells in group (0,12) at Month 18.
    - HPV-18 specific CD4+ T cell responses was 99.0 cells per million CD4+ T cells in group (0,12) at pre time point and 1165.5 cells per million CD4+ T cells in group (0,12) at Month 18.

- Overall, B cell responses (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) were as follows:
    - The HPV-16 specific memory B cells responses was 1.0 cells per million memory B cells at pre time point and 797.0 cells per million memory B cells in group (0,12) at Month 18.

    - The HPV-18 specific memory B cells responses was 1.0 cells per million memory B cells at pre time point and 582.0 cells per million memory B cells in group (0,12) at Month 18.

- During the follow-up period up to Month 18 (TVC),
    - 53 subjects reported at least one SAE (none were fatal).
    - 322 subjects reported at least one MSC.
    - 2 subjects reported at least one pIMD in group (0,12).

In conclusion, non-inferiority of immune responses to both HPV-16 and HPV-18 antigens was demonstrated at Month 18 when GSK Biologicals' HPV-16/18 vaccine was administered according to a 2-dose schedule of 0,6 months in 9-14 year old females, compared to the administration of HPV-16/18 vaccine according to the standard 3-dose schedule at 0,1,6 months in 15-25 year old females.

Non-inferiority of immune response to both HPV-16 and HPV-18 antigens was also demonstrated one month post the last vaccination when GSK Biologicals' HPV-16/18 vaccine was administered according to a 2-dose schedule of 0,12 months in 9-14 year old females, compared to the administration of HPV-16/18 vaccine according to the standard 3-dose schedule at 0,1,6 months in 15-25 year old.

In addition, non-inferiority of immune response to both HPV-16 and HPV-18 antigens was also demonstrated at Month 18 when GSK Biologicals' HPV-16/18 vaccine was administered according to a 2-dose schedule of 0,12 months in 9-14 year old females, compared to the administration of HPV-16/18 vaccine according to the 2-dose schedule at 0,6 months in 9-14 year old females.

The HPV-16/18 L1 VLP AS04 vaccine, administered at different schedules (0,6-months or 0,12- months in 9-14 year old healthy females or 0,1,6-months in 15-25 year old healthy females) had an acceptable safety profile in all groups in the follow-up period up to Month 18.

3. Rapporteur's overall conclusion

The MAH discussion and overall conclusion are endorsed. The results are in line with expectations. No further actions are required for this FUM/PAM at Month 18. The final results of this study (month 36) are expected as soon as possible.

☒ PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: