

## Statistical Review and Evaluation

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**Subject** STN: BL 125259/132 – Supplement: Prior Approval - Addition of 9-year old girls to "Indications and Usage"  
Cervarix (Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant)  
GlaxoSmithKline Biologicals

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### Executive Summary

CERVARIX (Human Papillomavirus [Types 16 and 18] Monophosphoryl Lipid A Vaccine, Adsorbed) was licensed on October 16, 2009. The approval letter advised the applicant of the requirement to perform a pediatric post-marketing study in females 9 years of age and noted the applicant's commitment to submit the final clinical study report for the aforementioned post-marketing study by June 30, 2010.

In order to meet the June 30 deadline, the required study report was previously submitted on June 17, 2010 to BLA 125259 as “General Correspondence”. The report is titled: “Supplemental Report to Clinical Study Report for Study 110659 (HPV-048): Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals’ HPV vaccine 580299 when administered in healthy females aged 9 - 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing.”

Study HPV-048 is a non-IND phase I/II, partially-blind, randomized, multicenter, age-stratified, dose-range study in healthy females aged 9 – 25 years to assess the safety and immunogenicity of CERVARIX vaccine administered intramuscularly according to a 2-dose schedule (0,2-month or 0,6-month) when compared to a standard 3-dose schedule.

A *post-hoc* analysis was performed to assess non-inferiority of the immune response after the third dose of CERVARIX (administered at Months 0, 1, 6) in 9-14 year old subjects vs. 15-25 year old subjects from HPV-048.

Non-inferiority of *Cervarix* in 9-14 year old subjects vs. 15-25 year old subjects with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated, since the lower limit of the 95% CI of the GMT ratio for subjects 9-14 years vs. 15-25 years was above the pre-defined limit of 0.5. Non-inferiority assessment data obtained from the analysis of the TVC were consistent with those obtained from the ATP cohort for immunogenicity.

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## I. BACKGROUND

The Biologics License Application (BLA) for CERVARIX [Human papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant] was approved on October 16, 2009 for use in females 10 through 25 years of age. CERVARIX is indicated for the prevention of the following diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18: cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma *in situ*, and cervical intraepithelial neoplasia (CIN) grade 1.

The October 16, 2009 approval letter advised the applicant of the requirement to perform a pediatric postmarketing study in females 9 years of age, pursuant to Section 505B(a) of the Food Drug and Cosmetic Act and noted the applicant's commitment to submit the final clinical study report for the aforementioned postmarketing study by June 30, 2010.

In order to meet the June 30 deadline, the required study report was previously submitted on June 17, 2010 to BLA 125259 as "General Correspondence". The report is titled: "Supplemental Report to Clinical Study Report for Study 110659 (HPV-048): Evaluation of the safety and immunogenicity of GlaxoSmithKline Biologicals' HPV vaccine 580299 when administered in healthy females aged 9 - 25 years using an alternative schedule and an alternative dosing as compared to the standard schedule and dosing."

Because Study HPV-048 remains ongoing, it is still blinded to GSK. Therefore, an external statistician was needed to prepare the datasets and provide them to the applicant through a firewall group. This was completed in August 2010. The datasets are being provided in a separate firewall submission to this supplemental application.

The HPV-048 supplemental study report presents *post-hoc* immunogenicity analyses requested by CBER to fulfill the pediatric study requirements for Cervarix in females 9 years of age and supplements the HPV-048 Month 7 Clinical Study Report, dated March 20, 2009. These two study reports are provided in this submission.

This review focuses on the post-hoc immunogenicity analyses.

## II. STATISTICAL EVALUATION

### II.1 Overview of Study HPV-048

#### Study Design

Study HPV-048 is a non-IND phase I/II, partially-blind, randomized, multicenter, age-stratified, dose-range study in healthy females aged 9 – 25 years to assess the safety and immunogenicity of CERVARIX vaccine administered intramuscularly according to a 2-dose schedule (0,2-month or 0,6-month) when compared to a standard 3-dose schedule.

The study is being conducted in Canada and Germany. A total of 960 subjects were vaccinated and 922 subjects completed the active phase of the study (Month 0 to Month 7). Currently, the study is still ongoing up to Month 24.

In the study, the four treatment groups received HPV-16/18 L1 VLP AS04 at different dosages (20 µg or 40 µg of each HPV antigen) and on different schedules (0,2-month, 0,6-month or 0,1,6-month schedules) (Table 1, same as Table 1 in HPV-048 supplemental Report). Each group was stratified into three age strata with 80 subjects planned to be enrolled in each stratum.

**Table 1 Study design summary**

| Group*           | HPV-16/18 dosages (µg/µg) | Schedules   | Age strata (years) | N   |
|------------------|---------------------------|-------------|--------------------|-----|
| 40/40 M 0,2      | 40/40                     | 0,2-month   | 9 - 14             | 80  |
|                  |                           |             | 15 -19             | 80  |
|                  |                           |             | 20-25              | 80  |
| 40/40 M 0,6      | 40/40                     | 0,6-month   | 9 - 14             | 80  |
|                  |                           |             | 15 -19             | 80  |
|                  |                           |             | 20-25              | 80  |
| 20/20 M 0,6      | 20/20                     | 0,6-month   | 9 - 14             | 80  |
|                  |                           |             | 15 -19             | 80  |
|                  |                           |             | 20-25              | 80  |
| Cervarix M 0,1,6 | 20/20                     | 0,1,6-month | 9 - 14             | 80  |
|                  |                           |             | 15 -19             | 80  |
|                  |                           |             | 20-25              | 80  |
| Total            |                           |             |                    | 960 |

\*For blinding within these groups, a placebo (aluminum hydroxide [Al(OH)<sub>3</sub>]) was administered at Month 6 (Group 40/40 M0,2) or at Month 2 (Groups 40/40 M0,6 and 20/20 M0,6). **The Cervarix M0,1,6 group was not blinded.**

During the active phase of the study, a subset of 9-14 year old subjects in Study HPV-048 received CERVARIX according to the standard schedule.

Following the FDA review of the Pediatric Research Plan included in the BLA for CERVARIX, a *post-hoc* analysis was requested to assess non-inferiority of the immune response after the third dose of CERVARIX (Months 0, 1, 6) in subjects 9-14 years vs. subjects 15-25 years. The submitted annex report presents the results of the *post-hoc* non-inferiority analysis.

## II.2 Post-hoc Analysis

A *post-hoc* analysis was performed to assess non-inferiority of the immune response after the third dose of CERVARIX (administered at Months 0, 1, 6) in 9-14 year old subjects vs. 15-25 year old subjects. Non-inferiority of the immune response was to be

demonstrated if the lower limit of the 95% confidence interval (CI) of the GMT ratio of the 9-14 year old subjects over the 15-25 year old subjects was above the pre-defined limit of 0.5.

### Study Population

The non-inferiority assessment was performed on the According-To-Protocol (ATP) cohort for immunogenicity and the Total Vaccinated cohort (TVC).

The ATP cohort for post-hoc analysis of immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This cohort included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component after vaccination and pre-vaccination serostatus were negative.

The Total Vaccinated cohort included all vaccinated subjects. Thus, the Total Vaccinated cohort for post-hoc analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available and their pre-vaccination serostatus were negative. The Total Vaccinated cohort analysis was performed per treatment actually administered.

### **II.3 Analysis Results**

Non-inferiority of CERVARIX in 9-14 year old subjects vs. 15-25 year old subjects with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated, since the lower limit of the 95% CI of the GMT ratio for subjects 9-14 years vs. 15-25 years was above the pre-defined limit of 0.5 (Table 2). Age stratified seropositivity rates for anti-HPV-16 and HPV-18 antibody titers by age group are also shown in Table 2.

**Table 2 Seropositivity, geometric mean titers (GMT) and GMT ratios for the anti-HPV-16 and anti-HPV-18 response to Cervarix in 9-14 year old subjects and 15-25 year old subjects, one Month Post Dose 3 (ATP cohort for Immunogenicity)**

|             | Cervarix 3-dose (Months 0, 1, 6) |                               |                            |                      |                            |                            | GMT ratio<br>(9-14 yrs/<br>15-25 yrs)<br>(95% CI)) |
|-------------|----------------------------------|-------------------------------|----------------------------|----------------------|----------------------------|----------------------------|--|
|             | Subjects 9-14 years              |                               |                            | Subjects 15-25 years |                            |                            |  |
|             | N                                | GMT<br>(95% CI)               | % Seropositive<br>(95% CI) | N                    | GMT<br>(95% CI)            | % Seropositive<br>(95% CI) |  |
| Anti-HPV-16 | 67                               | 22261.3<br>(18033.6, 27480.0) | 100%<br>(94.6, 100)        | 111                  | 10322<br>(8329.2, 12791.5) | 100%<br>(96.7, 100)        | 2.16<br>(1.57, 2.97)                               |
| Anti-HPV-18 | 68                               | 7398.8<br>(6033.3, 9073.4)    | 100%<br>(94.7, 100)        | 114                  | 4261.5<br>(3572.0, 5084.1) | 100%<br>(96.8, 100)        | 1.74<br>(1.32, 2.29)                               |

GMT = geometric mean antibody titer

N = Number of subjects with pre-vaccination seronegative results (antibody titer < 8 ELU/ML for HPV-16; antibody titer < 7 ELU/ML for HPV-18)

95% CI = 95% confidence interval

Seropositive = Antibody titer ≥ 8 ELU/ML for HPV-16; antibody titer ≥ 7 ELU/ML for HPV-18

*Reviewer's comments: 1) Table 2 which was constructed by me and all numbers in this table have been checked by me using SAS programs based on the applicant submitted data. 2) Please note that ATP cohort for this post-hoc analysis included the subjects with pre-vaccination seronegative results.*

Non-inferiority assessment data obtained from the analysis of the TVC were consistent with those obtained from the ATP cohort for immunogenicity and are provided in [Table 3](#). Age stratified seropositivity rates for anti-HPV-16 and HPV-18 antibody titers by age group are also presented in [Table 3](#).

**Table 3 Seropositivity, geometric mean titers (GMT) and GMT ratios for the anti-HPV-16 and anti-HPV-18 response to Cervarix in 9-14 year old subjects and 15-25 year old subjects, one Month Post Dose 3 (Total Vaccinated Cohort)**

|             | Cervarix 3-dose (Months 0, 1, 6) |                               |                            |                      |                             |                            | GMT ratio<br>(9-14 yrs/15-25 yrs)<br>(95% CI)) |
|-------------|----------------------------------|-------------------------------|----------------------------|----------------------|-----------------------------|----------------------------|--|
|             | Subjects 9-14 years              |                               |                            | Subjects 15-25 years |                             |                            |  |
|             | N                                | GMT<br>(95% CI)               | % Seropositive<br>(95% CI) | N                    | GMT<br>(95% CI)             | % Seropositive<br>(95% CI) |  |
| Anti-HPV-16 | 74                               | 22348.2<br>(18290.9, 27305.5) | 100%<br>(95.1, 100)        | 126                  | 9684.4<br>(7920.3, 11843.8) | 100%<br>(96.7, 100)        | 2.31<br>(1.70, 3.12)                           |
| Anti-HPV-18 | 74                               | 7321.5<br>(6033.7, 8884.1)    | 100%<br>(95.1, 100)        | 129                  | 3933.2<br>(3360.4, 4745.2)  | 100%<br>(97.2, 100)        | 1.83<br>(1.40, 2.40)                           |

GMT = geometric mean antibody titer

N = Number of subjects with pre-vaccination results available

95% CI = 95% confidence interval

Seropositive = Antibody titer ≥ 8 ELU/ML for HPV-16; antibody titer ≥ 7 ELU/ML for HPV-18

*Reviewer's comments: 1) Table 3 was constructed by me and all numbers in this table have been checked by me using SAS programs based on the applicant submitted data. 2) Please note that TCV cohort for this post-hoc analysis included the subjects with pre-vaccination seronegative results.*

#### II.4 Gender, Race, and Other Subpopulations

The study population for this post-hoc analysis included females only and majority of them were white (97.5%). Data analyses were performed by age strata (9-14 and 15-25 year-old).

#### II.5 Conclusions

Non-inferiority of *Cervarix* in 9-14 year old subjects vs. 15-25 year old subjects with respect to anti-HPV-16 and anti-HPV-18 GMTs was demonstrated, since the lower limit of the 95% CI of the GMT ratio for subjects 9-14 years vs. 15-25 years was above the pre-defined limit of 0.5.

### **III. COMMENTS TO THE REVIEW COMMITTEE**

- In an internal meeting dated October 25, 2010, it was decided that the post-hoc analysis is sufficient to support the requirement for a pediatric post-marketing study in females 9 years of age.
- Please note that the study cohorts (ATP and TVC) in this post-hoc analysis excluded the subjects with pre-vaccination seropositive results.
- Please note that the safety profile of this post-marketing post-hoc study is assessed by the epidemiological and clinical reviewers.

### **IV. COMMENTS TO THE APPLICANT**

None

### **V. REVIEWER'S RECOMMENDATION**

The post-hoc analysis showed that the immune response with respect to anti-HPV-16 and anti-HPV-18 after the third dose of CERVARIX (administered at Months 0, 1, 6) in 9-14 year old subjects is non-inferior to that in 15-25 year old subjects. The internal meeting dated October 25, 2010 decided that the post-hoc analysis would be sufficient to support the requirement for a pediatric post-marketing study in females 9 years of age.