

Record of Telephone Conversation - Cervarix, September 10, 2008

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RECORD OF TELEPHONE CONVERSATION

Submission Type: Original Application Submission ID: 125259/0 Office: OVR

Product:

Human Papillomavirus Vaccine, AS04 Adjuvant-Adsorbed

Applicant:

GlaxoSmithKline Biologicals

Telecon Date/Time: 10-SEP-2008 12:00 AM

Initiated by FDA? Yes

Telephone Number:

Communication Category(ies):

Advice

Author: HELEN GEMIGNANI

Telecon Summary:

CBER response to 29-Jul-2008 proposal describing format and content of HPV-008 final study report and the supplemental safety information to be included in the Class 2 Resubmission.

FDA Participants:

Non-FDA Participants:

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

To: Matthew Whitman and Cynthia D'Ambrosio

File: BLA STN 125259/0 - CERVARIX

RE: Response to your BLA Amendment Dated July 29, 2008

Date: September 10, 2008

The following comments are in response to your July 29, 2008, submission to your CERVARIX BLA where you requested CBER comments on your proposed Class 2 Resubmission.

1. Your plan to separate efficacy analyses of HPV-008 into Part 1 and Part 2 is not acceptable. CBER requires that all available information and analyses be submitted in one submission at the time the clock re-starts, especially in light of the 6 month review time frame (with a VRBPAC estimated to occur at 4 – 4.5 months into the cycle). CBER is concerned that incomplete data will be available at the time of licensure based on this 2-part submission, and this could potentially impede progress in proceeding towards final action on this BLA.
2. You indicated that an exploratory endpoint will include histopathologically confirmed CIN 2+ regardless of HPV DNA in lesion and stratified according to subjects' baseline HPV DNA status. CBER requests exploratory analyses of efficacy against CIN 2+ related to ANY HPV type be submitted within the HPV-008 report in all vaccinated subjects, regardless of baseline Pap test and/or baseline PCR status.
3. The impact of non-vaccine HPV types is important to consider the overall public health benefit. Please include analyses of efficacy in prevention of CIN2+ associated with non-vaccine HPV types in subjects who were naïve for the relevant non-vaccine HPV type, in subjects non-naïve for the relevant non-vaccine HPV type, in all subjects regardless of baseline HPV DNA status and regardless of cytology, and in subjects naïve for all tested HPV types (seronegative and PCR negative for HPV 16 and 18; and PCR negative for the tested non-vaccine HPV types) with a normal cytology at baseline.
4. Histopathologically confirmed CIN 2+ associated with HPV 16 or HPV 18, postdose 1, in women HPV 16 or 18 naïve (by PCR) with a normal cytology at Month 0 will be provided as part of additional analyses requested by CBER. Please perform a similar analysis in subjects who are seronegative AND PCR negative for these vaccine HPV types with a normal cytology.
5. CBER requests that exploratory analyses that were provided in the original HPV-008 report (125259/0), in women who were seropositive and PCR positive, seronegative and PCR positive, and seropositive and PCR negative for the relevant HPV type be submitted within the HPV-008 report.

6. CBER requests that you present all CIN 2+ cases (as identified by the pathology panel) for each treatment group in the following table format:

PID (Site, age years)	Date of first exam	Pap at baseline	PCR Month 6 (Pap M6 if abnormal)	PCR Other times During study	PCR Lesion	Date of CIN 2+ (mo. to dx)
1154 (US, 18)	4/18/05		Neg.	12/19/05: +16 7/3/06: +16	NO RESULT	8/25/06 (16 mo)

(This includes a sample case from the original data submitted in 2007).

In this table, please include all HPV types detected for the subject during the study, and specify if the lesion is CIN 2 or CIN 3 or other (i.e., AIS).

7. The plan for the meeting to present additional data on the adjuvant, as well as the plan to submit expert reports on musculoskeletal events and congenital anomalies prior to Class 2 Resubmission is acceptable.

8. The plan to submit other safety data from the post-marketing experience in EU and other countries is acceptable.

9. For the safety data that will be provided for study HPV-008, please confirm that the occurrences of all adverse events listed will be reported overall AND stratified.

10. For immunogenicity endpoints, the principal analyses will be conducted in the ATP cohort for immunogenicity in all evaluable subjects (those meeting all eligibility criteria, non-violators, with no elimination criteria) for whom data concerning immunogenicity endpoints are available for antibodies against at least one vaccine component after vaccination. Subjects who acquired either HPV 16 or 18 infection during the trial will be excluded from ATP cohort for immunogenicity. CBER requests that you provide this analysis in all subjects tested, regardless of whether they acquired an infection with HPV 16 or 18.

11. You state that HPV 16 and HPV 18 ELISA titers and seroconversion rates at Months 6, 7, 12, and 24 (in the immunogenicity subset) will be provided. These analyses will be stratified according to initial HPV 16 or 18 serostatus. Please provide an analysis in subjects who were seropositive to the relevant HPV type at baseline as well.

12. You state that if a sufficient number of subjects are available, HPV 16 and 18 seroconversion will be assessed in vaccine recipients with breakthrough HPV 16 or 18 infection and HPV 16 or 18 neoplasias and compared with selected non-cases (vaccine recipients without persistent infection or neoplasia matched for age, race, and clinical site). These analyses are restricted to subjects who are seronegative for the relevant HPV type at baseline. Please also provide available immune responses in any subject with a breakthrough case. In addition, please confirm that the term “neoplasias” refers to cervical dysplastic lesions, i.e., CIN 2+.