

Memorandum

To Helen Gemignani
Robin Levis, Ph.D.
Martha Lee, Ph.D.

From Nancy Miller, M.D,
CBER/OVRR/DVRPA/VCTB

Through Joseph Toerner, M.D., M.P.H.
Team Leader, Vaccines Clinical Trial Branch

Subject BLA (STN 125259/0.39) Cervarix (Human Papillomavirus Vaccine, AS04 Adjuvant Adsorbed)
- Request for comment on proposals for Class 2 resubmission

At a recent Type B meeting on 6/24/08, between CBER and GlaxoSmithKline to discuss the BLA for Cervarix (HPV 16/18 VLP L1 vaccine, adjuvanted with AS04), GSK advised that they were voluntarily postponing the re-start of the review clock in order to incorporate the final analyses of key data for clinical study HPV-008 into the pending BLA. In this amendment, GSK is submitting proposals describing the format and contents of the HPV-008 report and supplemental safety information for review.

The sponsor has proposed that the report is planned in two parts: the Main Report (Part I) and an Addendum Report (Part 2). The specific endpoints to be included in each part, as well as the schedules for submission are described in this amendment. They also include a supplement to the BLA Cumulative Safety Update, and the specific safety endpoints with identification are provided in a proposal for the supplement to the BLA cumulative safety update. They also indicate that the post-marketing surveillance, commercial distribution, and IND safety report information are addressed.

Reviewer's Comment: From the FDA Guidance "Classifying Resubmissions in Response to Action Letters", the following is stated: "...*resubmission* refers to a complete response to an action letter on an original NDA or LA: a submission that purports to answer all of the deficiencies that needed to be addressed by the applicant prior to approval of the original application as set forth in a previous action letter (approvable, not approvable, or complete response letter)." The internal goal date for responding to such a submission is 6 months.

Items to be provided in advance of the class 2 resubmission:

1. Meeting request and briefing document for a Cervarix adjuvant scientific meeting.
This meeting is on the schedule for 10/24/08, and GSK will provide further scientific data regarding the adjuvant used in this vaccine, AS04, which contains aluminum hydroxide and monophosphoryl lipid A.

2. Final expert reports in support of safety update provided in response to the CR letter of 12/14/07, to include reports on musculoskeletal events and congenital anomalies.
3. Proposal to update CMC/technical section to provide updated cumulative stability data in the class 2 resubmission.

Reviewer's Comment: The plan for the meeting and expert reports on musculoskeletal events and congenital anomalies is acceptable.

Items to be provided in class 2 resubmission (clock re-start):

1. HPV-008 final analysis report: A proposal for this is included.
2. Supplemental safety data: a proposal for this is included. These data will serve to update the safety information of the BLA's cumulative Safety Update current through 9/30/07 or 12/31/07, depending on the endpoint, with at least an additional 6 months of date.
3. Final study report of HPV-007 (36 months) to be provided as an addendum to CR Question 9. This report also to be submitted to IND -(b)(4)-.
4. Revised prescribing information to reflect final efficacy data and updates safety information.
5. CMC updates as agreed based on the GSK proposal submitted during 8/08. (Per product reviewer).

Regarding Item #1 (HPV-008 study report proposal) in items to be provided in class 2 resubmission, the sponsor proposes to submit this final study report in 2 parts. They indicate that the main report will be provided at the time the review clock for BLA 125129 is restarted with reflection of the findings in a revised package insert, and the report addendum will be available 12-16 month later (i.e., 3-4 months into the 6 month clock, which would be at the time of VRBPAC but prior to action due date).

In the Main Report (Part 1), GSK will provide data for the following primary and secondary endpoints, and the principal analyses of efficacy will be performed in the ATP cohort for efficacy. Analyses will also be performed for the TVC-1 cohort.

- The ATP cohort includes subjects who receive all 3 doses of vaccine, have a normal or low-grade cytology (\leq LSIL) at Day 1, and for whom efficacy data are available. These subjects must be negative for HPV DNA (by PCR) at Month 0 and 6 for the corresponding HPV type in the analysis, and the follow-up time starts the day after Dose 3.
- The TVC-1 cohort includes all vaccinated subjects (at least one dose) for whom data are available, and who had a normal or low grade cytology at Month 0. These subjects must be negative for the HPV types at month 0 for the corresponding HPV type in the analysis, except for the endpoints evaluated in HPV DNA positive women at Month 0. Cases will be counted starting the day after Dose 1.

Reviewer's Comment: CBER requests that the exploratory analyses that were provided in the original HPV-008 report, in women who were seropositive and/or PCR positive for the relevant HPV type should also be submitted. In addition, analyses including CIN 2+ related to any HPV type will need to be included in the study report. The impact of non-vaccine HPV types is important to consider the overall public health benefit.

The endpoints that will be analyzed and provided in Part 1 are as follows:

Primary endpoint: Histopathologically confirmed CIN 2+ associated with HPV 16 or HPV 18 detected within the lesional component of the cervical specimen by PCR, overall and stratified according to Month 0 HPV 16 or HPV 18 serostatus. VE and 96.1% CIs will be calculated.

Virological secondary endpoints:

- 12 month persistent infection with HPV 16 or HPV 18 by PCR, overall and stratified according to initial HPV 16 or HPV 18 serostatus.
- 6 month persistent infection with HPV 16 or HPV 18 by PCR, overall and stratified according to initial HPV 16 or HPV 18 serostatus.
- 6 month persistent infection with with the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.

Histopathological secondary endpoints:

- Histopathologically confirmed CIN 2+ associated with the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 detected within the lesional component of the cervical specimen by PCR.
- Histopathologically confirmed CIN 1+ associated with HPV 16 or HPV 18 detected within the lesional component of the cervical specimen by PCR, overall and stratified according to Month 0 HPV 16 or HPV 18 serostatus.
- Histopathologically confirmed CIN 1+ associated with the following oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 detected within the lesional component of the cervical specimen by PCR.

For all histopathological outcomes, an exploratory analysis referred to as “HPV type assignment algorithm” will be assessed. This analysis will consider lesions with more than one HPV type to be related to a vaccine HPV type only if that type was present on 2 prior samples.

Reviewer’s Comment: CBER has commented on this analysis previously. The sponsor had wanted to use this method of assessing cases in their primary analysis, but CBER did not agree, and at most, CBER advised that this method could be used in exploratory analyses.

Exploratory endpoints:

- 12 month persistent infection with the non-vaccine oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.
- Histopathologically confirmed VIN1+ or VaIN1+ (combined endpoints) associated with HPV 16 or HPV 18 detected within the lesional component of the cervical specimen by PCR, overall and stratified according to Month 0 HPV 16 or HPV 18 serostatus.
- Histopathologically confirmed CIN 2+ regardless of HPV DNA in lesion and stratified according to subjects’ baseline HPV DNA status.

Reviewer’s Comment: CBER is interested in this analysis, in subjects who are naïve and non-naïve for any HPV type.

The endpoints below will be provided as tables from statistical output in an annex to the Part I report (additional analyses requested by CBER).

- Histopathologically confirmed CIN 2+ associated with HPV 16 or HPV 18, postdose 1, in women with a history of the corresponding HPV type (seropositive and/or PCR positive at baseline) and with a normal or low-grade cytology at Month 0).

Reviewer's Comment: Please provide a similar analysis in women with any grade cytology at baseline.

- Histopathologically confirmed CIN 2+ associated with HPV 16 or HPV 18, postdose 1, in women who were DNA negative for HPV 16 or 18 and have a normal cytology.

Reviewer's Comment: Please perform a similar analysis in subjects who are seronegative AND PCR negative for the vaccine HPV types.

- Histopathologically confirmed CIN 2+ associated with the oncogenic HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, postdose 1, in women who were HPV 16 and 18 DNA negative and have a normal cytology at Month 0.

Reviewer's Comment: Please include an additional analysis for these non-vaccine HPV types for women naïve for the relevant non-vaccine HPV type, as well as an analysis in women naïve for ALL tested oncogenic HPV types at Month 0 (i.e., PCR negative for non-vaccine HPV types and seronegative/PCR negative for the vaccine HPV types), with a normal cytology and in those with any cytology.

- The proportion of subjects with a CIN 2+ diagnosed as a result of an abnormal cytology at baseline.
- Histopathologically confirmed CIN 2+ associated with HPV 16 and/or 18 regardless of baseline HPV DNA status.

Reviewer's Comment: As noted above, CBER requests that CIN 2+ associated with ANY HPV in the entire study population who received at least 1 dose.

Safety

- Solicited local or general symptoms within 7 days after each dose, and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in a subset of subjects from select study sites (N≥4000, or app. 1000 per region).
- Unsolicited symptoms within 30 days of vaccination after any dose and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in a subset of subjects from select study sites (N≥4000, or app. 1000 per region).
- SAEs throughout the entire study period (Month 0 to 48) and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in all subjects.
- AEs leading to discontinuation throughout the entire study period and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in all subjects.
- New onset chronic diseases throughout the entire study period and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in all subjects.
- Medically significant conditions throughout the entire study period and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in all subjects.
- Outcome of all pregnancies throughout the entire study period, overall and stratified by initial HPV 16/18 DNA status and according to HPV 16/18 serostatus in all subjects.

Reviewer's Comment: Please confirm that the occurrences of all adverse events listed will be reported overall AND stratified.

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.

- HPV 16 and HPV 18 ELISA titers and seroconversion at Months 6, 7, 12, and 24 (in the immunogenicity subset). These analyses will be stratified according to initial HPV 16 or 18 serostatus.
- 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.

Reviewer's Comment: An analysis of immune response in all subjects in whom data are available should also be provided, regardless of whether they do or do not develop persistent infection or dysplasias. It is of interest to have available immune response in any subject with a breakthrough case. In addition, please confirm that analyses will be provided overall AND stratified.

Addendum report includes the following remaining exploratory efficacy endpoints:

- Histopathologically confirmed VIN1+ or VAIN1+ (combined endpoint) associated with the following oncogenic HPV types detected within the lesional component of the tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68.
- Histopathologically confirmed VIN1+ or VAIN1+ (combined endpoint), irrespective of HPV DNA results found in the lesional component of the tissue specimen.
- Incident infection with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- Incident infection with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (by PCR).
- Histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 detected in the preceding cytological specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA). Preceding cytological specimen is defined as the last cervical cytology specimen collected before the histopathology specimen was obtained.
- Histopathologically confirmed CIN1+ or CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the tissue specimen (by PCR) in women infected prior to vaccination with the corresponding HPV type, i.e. positive for HPV DNA (by PCR) at Month 0, and with a normal or low-grade

cytology (negative or ASC-US or LSIL) at Month 0, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

- Histopathologically confirmed CIN2+ associated with cervical infection by HPV-16 only, HPV-18 only or HPV-16 and HPV-18 only (by PCR) within the lesional component of the tissue specimen, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Any cytological abnormality associated with HPV-16/18 or with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 (by PCR).
- Histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR) in women with a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0, irrespective of their baseline HPV DNA status.
- Clearance of HPV-16 or HPV-18 cervical infection (by PCR) in women infected prior to vaccination with the corresponding HPV type, i.e., positive for HPV DNA (by PCR) at Month 0, and with a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).

Clearance is defined as the first negative sample for HPV DNA (by PCR) for the corresponding HPV type after Month 0, after which no positive samples occur. Subjects that are double HPV DNA positive are cleared if they have a negative sample for either HPV-16 or HPV-18.

- Persistent infection (6-month definition) with HPV-16 and/or HPV-18 (by PCR) in women with a history of infection with the other vaccine type (HPV DNA positive and/or seropositive) prior to vaccination.
- Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR) in women who received only two doses of the study vaccine, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Incident infection with HPV-16 or HPV-18 (by PCR) in women who received only two doses of the study vaccine, overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
- Administration of local cervical therapy (LEEP, CONE, KNIFE or LASER), irrespective of baseline HPV DNA status.

Reviewer's Comment:

The sponsor's plan to separate efficacy data is not acceptable. Based on experience with not having all information and analyses readily available and easily reviewable at the time of study submission, especially in light of the 6 month time frame (with a VRBPAC estimated to occur at 4 – 4.5 months into the cycle), CBER requests that there be one submission with all analyses provided.

CBER also notes that annex reports complicates the review process, in that data from one trial are presented in several documents, instead of being presented cohesively in one document.

Proposal for Supplement to BLA Cumulative Safety Update

This supplement will serve to update the safety information of the BLA cumulative Safety update, now current through 9/30/07 or 12/31/07, depending on the endpoint. It will be similar in scope to the data submitted in response to the CR letter comments of 12/14/07. A cumulative analysis of endpoints will be provided, but there will be no re-submission of CIOMS/International Events Reports already submitted. For ease of review, the cumulative analyses will identify new information relative to that provided in the BLA Safety Update. New events in an interval of time still to be determined (but providing no less than 6 months of additional safety data from the cut-off date of the last safety update) will be linked to the submitted CIOMS reports. The same cut-off date will apply for all categories of events in the supplement.

Since the overall safety data contains data from ongoing blinded studies (HPV-008, HPV-009, HPV-010, HPV-015, HPV-023, and HPV-032), the supplement will need to be managed and submitted via the Firewall team. All data will be provided in an unblended manner for CBER review. These will include the following:

Deaths from all studies in which Cervarix was administered (cut-off >6/30/08).

SAEs from all studies in which Cervarix was administered (cut-off >6/30/08).

Pregnancy outcomes (other than congenital anomalies) from 001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015 and 016 (cut-off >6/30/08).

Congenital anomalies from all studies in which Cervarix was administered (cut-off >6/30/08).

Medically significant AEs from 008, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015 and 016 (cut-off >6/30/08).

Study withdrawals due to AEs/SAEs 001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015 and 016 001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015 and 016 (cut-off >6/30/08).MPL meta-analysis with reanalysis for neuroinflammatory and musculoskeletal categories of events and analysis with new terms from experts in all studies involving MPL as part of adjuvant 001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015 and 016 (cut-off >6/30/08).

Reviewer's Comment: The proposal for safety submission appears comprehensive, and the sponsor states that the data will be provided in an unblended manner to CBER to expedite review.

Other safety data to include in package

Post-marketing exposure to Cervarix by the end of calendar year 2008 is estimated to be app. --(b)(4)-- doses distributed outside the US. A tabular listing by country can be provided. This listing can also be stratified by month. AE reports obtained through postmarketing surveillance can be provided to FDA possibly in listings similar to the IND annual report listings, with an accompanying document to summarize the cumulative safety experience (e.g., cumulative experience PSUR with data lock point of 11/17/08 being considered).

As INDSRs were requested to be submitted to the BLA, the team proposes to provide a summary listing of INDSRs up to the new data lock point with a cross-reference to the reporting of safety endpoints and events (where appropriate).

Reviewer's Comment: This is acceptable and is appreciated.

Comments for Sponsor:

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	4/18/05		Neg.	12/19/05: +16	NO	8/25/06

(US, 18)				7/3/06: +16	RESULT	(16 mo)
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(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+.