

## Memorandum

**Date** August 10, 2007

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**From** Martha Lee, Ph.D. *Martha Lee*  
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**Through** A. Dale Horne, Dr. P.H. *A. Dale Horne*  
Chief  
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**Subject** BLA (STN 125259/0.8) Cervarix (Human Papillomavirus Vaccine, AS04 Adjuvant Adsorbed)  
- Adverse events reported following administration of vaccines formulated with GSK's proprietary adjuvant systems containing MPL: proposed analytical plan

**cc:** HFM-478/Gopa Raychaudhuri  
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## Background

This amendment contains the sponsor's responses to CBER's request during a teleconference on July 18, 2007. The sponsor was asked to supply an analysis plan for a meta-analysis of adverse events related to inflammatory neurological disorders (SAEs, unsolicited AEs) and also those adverse events of potentially autoimmune etiology that are non-neurological, from all IND and non-IND studies which involve the use of MPL in humans from both GSK and Corixa sources.

## Statistical Review

Five sections are included in this analysis plan: 1) scope of the analysis, 2) case ascertainment, 3) evaluation of the potential cases of inflammatory neurological disorders and adverse events of potentially autoimmune etiology that are non-neurological, 4) analyses to be performed, and 5) points to consider in the analysis.

### Section 1: Scope of the analysis:

All INDs and non-INDs which involve the use of MPL in humans, in both GSK and Corixa products, will be included in this analysis. Table 1 presents an overview of all adjuvant systems

developed by GSK Biologicals or Corixa that contain MPL.

Table 1: Overview of all MPL-containing adjuvants evaluated in human clinical studies.

(b)(4)

Table 2 provides an overview of all clinical development programs from GSK Biologicals and Corixa in which MPL-containing products were injected in humans. This table also provides a general description of the study population for each project, the current development stage of the project, the number of subjects exposed to MPL-containing vaccines, and the number of subjects in the control groups in which MPL was not administered.

Among all clinical development programs, HPV vaccines, Herpes Simplex vaccine, and Hepatitis B Adjuvanted vaccine (Fendrix) are the three that are at late development stages and have large numbers of subjects exposed to MPL-containing vaccines (24,734; 15,629; and 3,430 for HPV, Herpes, and HBV, respectively).

Table 2: Overview of all clinical development from GSK Biologicals or Corixa in which MPL-containing products were injected into humans

Vaccine Development	Adjuvant System	Study Population	Development stage	Number of subjects exposed to MPL-containing vaccines*	Number of subjects in control groups
(b)(4)					
Hepatitis B Adjuvanted vaccine (Fendrix™)	AS04C	Adults	Late	3430	2068
(b)(4)					

Vaccine Development	Adjuvant System	Study Population	Development stage	Number of subjects exposed to MPL-containing vaccines*	Number of subjects in control groups
(b)(4)					
MPL- containing biologicals developed by Corixa **		Mostly Adults		1413	
<b>TOTAL</b>				55,532	39,017

## Section 2: Case ascertainment:

In general, the following safety information has been collected in the IND and non-IND studies which involve the use of MPL in humans from both GSK and Corixa sources:

- **Solicited adverse events:** The actively solicited events usually include events that are either expected to be related to vaccination (e.g., injection site reactions) or that are frequently seen after vaccination (more general reactions such as malaise or fever). None of the specific events requested by CBER for inclusion in the current analysis have been actively solicited. **Solicited events will therefore not be considered for this analysis.**
- **Unsolicited adverse events:** These include events that are reported to the investigator in an unsolicited manner by a subject in a study, usually at the time of a vaccination visit or follow-up visit. This category also includes serious adverse events (SAEs), which will be discussed separately. The follow-up period during which such non-serious unsolicited events are collected varies across projects and studies, but is usually a minimum of **one month after each dose**. The information collected for a non-serious unsolicited event is limited and includes the start/end dates of the event, a brief description of the event (e.g., the verbatim diagnosis or symptoms), its degree of severity, its outcome and a causality assessment. Information collected about an unsolicited event is entered in the clinical database and analyzed at study completion or at interim analysis.
- **Serious adverse events:** a serious adverse event (SAE) meets at least one of the following ICH criteria: **results in death, is life-threatening, requires hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring of a study subject, or is considered by medical judgment as medically significant.** It is expected

that a large proportion of the inflammatory neurological events requested by CBER to be included in the current analysis would be reported as SAEs. The information collected about an SAE includes elements such as the date on which the event occurred, onset time, description of the event, degree of severity, pre-existing medical history, concomitant medication, diagnostic tests, additional laboratory information, treatment and outcome. In addition, detailed narrative summaries of these cases are usually available. The information collected is to be provided to the sponsor's safety department within 24 hours and entered primarily in a separate safety database, as well as in the clinical database. Most SAE reports will lead to follow-up questions.

- Medically significant conditions and new onset of chronic diseases: In some protocols, "medically significant conditions" and "new onset of chronic diseases" have been collected. This is mainly the case for the phase III studies in the HPV and HSV projects. In these projects, "medically significant conditions" are defined as conditions prompting emergency room or physician visits that are not related to common diseases or routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervico-vaginal yeast infections, menstrual cycle abnormalities, and injury. "New onset of chronic diseases" is any event that an investigator considers to represent the new onset of a chronic disease. This group of events is collected in selected studies usually throughout the study duration. Of importance, the information collected for medically significant conditions and new onset chronic diseases is similar to that collected for unsolicited adverse events. More extensive information is available only if these events were also reported as SAEs.

The sponsor has previously analyzed the occurrence of adverse events of potentially autoimmune etiology in the adjuvanted HBV, HSV, and HPV programs. In these programs, screening for these events was done among all events reported as SAEs or unsolicited events. In some studies in the HPV program, screening for these events also occurred among events identified by the investigators or GSK as new onset of chronic diseases (as described above). As can be expected, events reported as an SAE are more severe in nature. All adverse events related to inflammatory neurological disorders as requested by CBER that have been identified to date in the HPV, HSV, and HBV programs (Guillain-Barré Syndrome, multiple sclerosis, optic neuritis, demyelinating events) were reported as SAEs.

As previously mentioned, GSK's adjuvant systems use MPL in different combinations of several components. It cannot be excluded that, were a true association to exist between MPL and any of the events of interest, this association would be influenced by other components and the specific formulation of the complete adjuvant system.

The sponsor therefore proposes to use the following ascertainment method for inflammatory neurological disorders and for adverse events of potentially autoimmune etiology that are non-neurological.

For the largest programs using AS04-adjuvanted vaccines (i.e., HPV, HSV, and Hepatitis B AS04), the sponsor will screen for inflammatory neurological disorders and for adverse events of potentially autoimmune etiology that are non-neurological among all reported

SAEs, all reported unsolicited events, and all reported events considered as new onset chronic diseases or medically significant conditions in studies in which the last two categories of events were also collected. The projects which will be analyzed as such are: HPV (HPV-16/18 L1 VLP AS04 vaccine, (b)(4)) (b)(4) HSV, and Hepatitis B AS04 (Fendrix™). As can be deduced from Table 2, these projects include approximately 79% of all subjects involved in GSK and Corixa trials with MPL-containing vaccines.

For all other projects, the sponsor will restrict the screening for potential inflammatory neurological disorders and for adverse events of potentially autoimmune etiology that are non-neurological to the reported SAEs. It is expected that restricting the analyses to the SAEs for these projects will result in negligible loss of information, given that:

- The overall contribution of these projects to the entire dataset is limited to approximately 20% of the subjects. Moreover, the average follow-up time in these projects is of relatively short duration compared with the studies in the HPV program, which typically involve longer term follow-up. A preliminary evaluation of all SAEs in MPL-containing vaccines has shown that less than 10% of adverse events of potentially autoimmune etiology were reported in these (non-AS04) projects.
- The populations exposed in the projects that do not rely upon AS04 as an adjuvant are quite heterogeneous and different from groups evaluated in programs with AS04. The two largest projects in the non-AS04 group are the malaria and adjuvanted influenza projects. The malaria project is a pediatric program conducted in Africa, where occurrence or ascertainment of most autoimmune diseases is expected to be very low. The influenza project is primarily conducted among elderly subjects, who have a different risk profile for the events of interest. Among the remaining projects, several are conducted in cancer patients for whom the risk profile of the events of interest is also expected to be different as compared to a healthy population.
- All of the inflammatory neurological disorders that were reported to date in the HSV, HPV, and HPV programs were reported as SAEs. It is unlikely that any of these severe disorders would be reported in a different manner in the projects that use MPL-containing adjuvants other than AS04.
- The available information routinely collected about unsolicited events not reported as SAEs is limited and does not allow for an assessment of the diagnostic certainty.
- No large comparative trials have been or are being conducted in projects that use MPL-containing adjuvants other than (b)(4). The contribution of the available trials of these projects to the overall analysis is therefore expected to be minimal.

The sponsor proposes to use the data lock point (DLP) of June 30, 2007 for the requested analysis. For some collaborative trials that are not directly supervised by GSK, an earlier data lock point may be used (any exceptions to the DLP of June 30, 2007 will be indicated in the final report).

*Reviewer's comment: The proposed data lock point (DLP) of June 30, 2007 appears reasonable, unless other reviewers have concerns about it.*

#### Events and Variables to be included in the current analysis

The Sponsor will screen for all events requested by CBER on July 10, 2007. The Sponsor has established the list of corresponding MedDRA codes that will be used for screening for these events. All events as requested and grouped by CBER on July 10, 2007 will also be considered as the outcomes of interest, with the following modifications proposed by the Sponsor:

- uveitis which was originally listed under the category 'Neuroinflammatory' is proposed to be listed under the category 'others'
- arthropathy, which is considered a very non-specific term and potentially related to a large variety of disorders, many of which not necessarily of autoimmune origin, is removed from the list of outcomes
- Addison's disease is proposed to be added under the category "others"
- Grave's and Basedow's refer to the same event.

As previously mentioned, the completeness of the reports varies with the reporting methods (SAEs, non-serious unsolicited symptoms, etc) and the availability of specific information (e.g., medical history, concomitant medications) is also expected to vary, depending on the reporting method. In general, the following variables will be collected for all subjects and events of interest:

- Study variables: study identifier
- Subject variables: subject identifier, treatment group, date of birth, gender, race/ethnicity, drop out, reason for drop out, last visit date
- Vaccination-related variables: number of doses administered and dates of administration, concomitant medication, and vaccinations
- Event-related variables: diagnosis, preferred term, verbatim term, date of onset seriousness category (serious, non-serious), treatment, hospitalization, outcome (including fatal), if fatal: cause and date of death, discontinuation of the investigative treatment country of reporting, time to onset since last vaccination, relevant medical history at study entry.

*Reviewer's comment: All variables listed above have been compared with the list which CBER previously sent to the sponsor. The proposed list of variables seems complete.*

The sponsor is currently considering how the treatment group assignments can be provided in the analyses without unnecessarily unblinding some of the subjects. The details of this procedure will be provided in the final report.

For SAEs, more detailed information is collected on several variables of interest. The following additional variables will be provided when available: pre-existing conditions, concurrent medication, duration of symptoms, laboratory tests, and diagnostic tests for diagnosis confirmation and outcome.

### Section 3: Evaluation of the potential cases of inflammatory neurological disorders and adverse events of potentially autoimmune etiology that are non-neurological

The diagnostic validity of the events reported is expected to be variable and will depend mostly on the complexity of the disease and diagnosis and the experience of the reporting investigators

or treating physicians. To ensure comparability of the findings across the projects and studies, the sponsor will also include an evaluation of the diagnostic validity of the reported cases of inflammatory neurological disorders, in addition to the all-encompassing analyses.

The objective of this evaluation is to classify the individual reports into three groups:

1. those reports that contain insufficient information to ascertain or refute the diagnosis
2. those reports that contain sufficient information to refute the diagnosis
3. those reports that contain sufficient information to agree with the diagnosis

For the last group, different levels of diagnostic certainty will be proposed. The sponsor intends to use an independent expert to perform the above evaluation. For these assessments the expert will be blinded to treatment group assessment. This evaluation will not be used in the main analyses, but will be primarily used in the exploratory observed/expected analyses and may also be included in any additional analyses (see Section 4).

*Reviewer's comment: This issue requires comments from the clinical reviewer, Dr. Nancy Miller.*

#### Section 4: Analyses to be performed

Analyses will be performed on each of the following datasets:

##### **Level 1 Analysis: Studies in the HPV vaccine program.**

Analyses of all IND and non-IND studies in the HPV vaccine program will be performed. These evaluations will include a search of all SAEs, unsolicited adverse events, medically significant events, and new onset of chronic diseases reported during the trials for events of interest. Of note, the (b)(4) will not be included in this dataset, as it represents a very limited number of subjects for whom safety data are available, including a minority who received AS04-adjuvanted vaccine.

##### **Level 2 Analysis: Studies in major AS04-adjuvanted vaccine programs.**

Analyses of all IND and non-IND studies in the 3 major programs which have evaluated vaccines adjuvanted with AS04 (HPV vaccine program, (b)(4) (b)(4) HSV, and adjuvanted HBV) will be performed. These evaluations will include a search of all SAEs and unsolicited adverse events (as well as medically significant events and new onset of chronic diseases when applicable) reported during the trials for events of interest.

##### **Level 3 Analysis: Studies in prophylactic programs using MPL-containing adjuvants.**

Analysis of all IND and non-IND GSK and Corixa studies, in all prophylactic programs which have evaluated vaccines with MPL-containing adjuvants, will be performed. This will include programs already described above as well as other (smaller) programs using MPL-containing adjuvants. In addition to the information specified for programs included in the level 1 and 2 analyses, only SAEs reported in other (smaller) prophylactic programs using MPL will be included in this analysis.



#### **Level 4 Analysis: Studies in therapeutic vaccine and cancer vaccine programs using MPL-containing adjuvants.**

Analysis of all IND and non-IND GSK and Corixa studies in all therapeutic vaccine and cancer vaccine programs which have used MPL-containing adjuvants will be performed. This analysis will be run separately, as many subjects included in these programs significantly differ from the healthy subjects included in other programs. SAEs reported in these programs will be included in this analysis.

*Reviewer's comment: We concur with the proposed analytical process.*

#### **Analytical methods**

Rate estimations by treatment group (MPL-containing or not) will be conducted on **pooled controlled studies, without adjustments**. To measure the potential effect of any difference in randomization ratios, a sensitivity analysis will be performed of the effect of excluding studies that have a randomization ratio different from 1:1. The inclusion of uncontrolled trials is not proposed for treatment specific rate estimates, as it is expected that such inclusion would result in biased estimates. Rates will be estimated by dividing the number of events by the number of subjects receiving at least one dose of vaccine in the study in which the event occurred. Incidence rates will be calculated for level 1 and 2 analyses and will be estimated by dividing the number of events by the cumulative mean follow-up time (in person-years) of all subjects receiving at least one dose of vaccine in the study in which the event occurred.

*Reviewer's comment: As the sponsor points out, there are limitations to the proposed pooling technique, even when restricted to the controlled trials (refer to Section 5). Thus, we recommend that the sponsor use a sufficiently advanced statistical procedure in conducting true meta-analyses.*

For each of the datasets described above the following outputs are proposed:

1. A comprehensive listing, by case, of all reported inflammatory neurological disorders and adverse events of potentially autoimmune etiology that are non-neurological, ordered by the groups proposed by CBER. For each case, the Sponsor will provide an overview of the available evaluation.
2. A comparative tabulation of the event rates (with 95% confidence interval) in the different treatment groups (MPL-containing or not), pooled across all controlled studies in the dataset. If any trials included in this pooled analysis have a randomization ratio different from 1:1, a similar table will be produced after exclusion of the unbalanced trials.
3. Additional exploratory analyses for inflammatory neurological disorders (observed/expected analyses): The incidence rates of inflammatory neurological disorders, across all trials, will be compared to the published background rate of

inflammatory neurological disorders. Given the uncertainty around the comparability of the observed rates and the (historical) background rates, this analysis is considered exploratory. The effect of certain variables such as age, gender, and geographic region may also be explored by performing stratified comparisons for events in which such stratum specific information has been published. The comparison will also take into account the level of diagnostic certainty that is most comparable between the observed rates and those applied in estimating the published background rates. Comparisons will also be made to unpublished information on the background rate of some inflammatory neurological disorders which the sponsor has obtained from a large health maintenance organization in the United States.

The sponsor may also perform additional analyses to further elucidate the outputs. Given the expected variability in the datasets and the potential complexity of the outputs, such analyses cannot be pre-defined at this stage. For inflammatory neurological disorders, the expert assessment may also result in additional analyses.

*Reviewer's comment: In view of the proposed pooled data analysis being inappropriate, the tables of the event rates, pooled across all controlled studies in the dataset, ought to be revised in order to be consistent with the future analytical plan.*

#### Section 5: Points to consider in the analysis

Sources of potential bias in this and other analyses will be reduced by pooling only controlled studies. There are, however, important limitations to the proposed pooling, even when restricted to the controlled trials. They include but are not limited to the following:

- The controls differ across the studies and include groups that received placebo, Hepatitis A vaccines and non-adjuvanted Hepatitis B vaccine. Whereas it is assumed that no association exists between any of these exposures and the events of interest, this cannot be excluded with certainty.
- The different studies vary with respect to other aspects such as the length of follow-up, the ascertainment of adverse events, and the population under investigation.
- In the level 2, 3, and 4 analyses, groups that received different MPL-containing adjuvants will be pooled. It cannot be excluded that, were a true association to exist between MPL and any of the events of interest, this association could be influenced by other components and the specific formulation of the complete adjuvant system.

Therefore, given the limitations of the data and data analyses, the overall outputs should be considered exploratory and not definitive.

*Reviewer's comment: A more advanced statistical approach may provide more reliable results. Whether the overall outputs should be considered exploratory will be decided by the review committee.*

**Recommendation:** We request a few revisions from the sponsor, detailed below.

**Comments and Questions to CBER:**

- The issue of diagnostic validity (Section 3, page 12) requires comments from the clinical reviewer, Dr. Nancy Miller.

**Comments and Questions to Sponsor:**

- You propose to perform “pooled” data analysis, in which specified adverse events (AEs) from different studies will be combined without accounting for the study effect. Please note that such pooled analyses are not true meta-analyses and therefore may be subject to biases, notably Simpson’s paradox, less inherent in true meta-analyses. Hence, the findings from the proposed pooled analyses could provide unreliable bases for regulatory decision-making. We therefore request that you perform appropriate meta-analyses rather than the proposed pooled analysis. Please acknowledge.
- Please also note that the proposed tables of the event rates across all controlled studies in the dataset need to be consistent with the revised analytical plan.