

Record of Telephone Conversation - Cervarix, October 14, 2009

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RECORD OF TELEPHONE CONVERSATION

Submission Type: Original Application Submission ID: 125259/0 Office: OVRP
Product:

Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant

Applicant:

GlaxoSmithKline Biologicals

Telecon Date/Time: 09-OCT-2009 12:27 PM

Initiated by FDA? Yes

Telephone Number:

Communication Category(s):

Other

Author: MICHAEL NGUYEN

Telecon Summary:

Response to Pregnancy Registry IR and PMC Commitment to submit 3mo Interim Reports

FDA Participants:

Non-FDA Participants:

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

From: nicholas.perombelon@gskbio.com [mailto:nicholas.perombelon@gskbio.com]

Sent: Friday, October 09, 2009 12:27 PM

Subject: Fw: Cervarix - Postmarketing Comments Follow Up and Request for Additional Information

Dear Lori,

Please find attached the GSK responses to the two questions you asked in your mail of October 7. We will also submit these responses to the Cervarix BLA.

Thanks and best regards,

Nicholas

Please provide the following additional information:

(a) study start and completion date and sample-size calculations (number of pregnancies, duration of study, and/or relative risk target) for the pregnancy registry

GSK Response

The purpose of the US-based Pregnancy Registry is to detect adverse pregnancy outcomes, including major teratogenic effects in the offspring of pregnant females intentionally or unintentionally exposed to Cervarix. The Registry is a program of enhanced pharmacovigilance that requires voluntary, prospective reporting of eligible pregnancies by patients and healthcare professionals. The intent of the Registry is to prospectively collect data describing exposure to Cervarix immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy.

The US-based Pregnancy Registry plans to detect adverse pregnancy outcomes in the offspring of pregnant females intentionally or unintentionally exposed to Cervarix.

Pregnancy outcomes of interest are: birth defects, live births, stillbirths, intrauterine fetal demise [death of conceptus at ≥ 20 weeks after the last menstrual period (LMP)], spontaneous abortion (death of conceptus at < 20 weeks after the LMP), and induced abortion.

The US-based Pregnancy Registry will be initiated immediately after vaccine licensure in the US. Entry of post-marketing reports into the Registry may therefore begin at the time of first commercial launch in the US (planned for November 2009).

The number of pregnant females who will be exposed to Cervarix is impossible to predict. It is proposed that Cervarix is classified as Pregnancy Category B and, therefore, the proposed Cervarix label includes the following wording: "Cervarix is not recommended for use in pregnant women or women planning to become pregnant during the vaccination course." The exposure will depend on several factors, including the uptake of the vaccine and the ages for which it will be recommended. During the first year of operation (1 June 2006 through 31 May 2007), the Gardasil Pregnancy Registry enrolled 461 reports; of these, only 19 had been reported prospectively and had estimated date of delivery (EDD) on or before the cut-off date of the report; three of the 19 pregnancies had been lost to follow-up. The second annual report included the cumulative experience (1 June 2006 through 31 May 2008). A total of 2149 reports of exposure to Gardasil; had been received; of these, 1440 met inclusion criteria for enrolment in the Registry, including 863 pregnancies for which outcomes were known. The sample sizes required to detect, with 80% power, various relative risks of spontaneous abortion were calculated using a 2-sided Fisher's exact test with $\alpha = 0.05$ (Software: --b(4)--). Because of the variation in literature-based estimates of the incidence of spontaneous abortion, the sample sizes required to detect various relative risks are presented in Table 1.

Table 1 Sample size calculation for reporting of spontaneous abortions in US-based pregnancy registry

| Proportion of Pregnancies resulting in Spontaneous Abortion | Relative Risk | Number of Registered Pregnancies Required |
|---|---------------|---|
| 8% | 2 | 125 |

| Proportion of Pregnancies resulting in Spontaneous Abortion | Relative Risk | Number of Registered Pregnancies Required |
|---|---------------|---|
| | 3 | 41 |
| | 5 | 35 |
| 14% | 2 | 67 |
| | 3 | 23 |
| | 5 | 15 |
| 20% | 2 | 41 |
| | 3 | 16 |
| | 5 | (Not applicable) |

Reports of birth defects will be reviewed individually and in aggregate and evaluated by timing of exposure, biological plausibility, target organ, expected population prevalence, etc.

Based on previous experience with pregnancy registries for similar products and in the interest of consistency among pregnancy registries for similar products, GSK proposes that the initial duration of the US-based Pregnancy Registry will be 5 years from licensure of Cervarix in the US with entry of post-marketing reports into the Registry beginning from the time of first commercial launch in the US (planned for November 2009). After reviewing the 5-year data, GSK would be willing to discuss the need to continue further the US-pregnancy registry for Cervarix.

(b) an agreement to provide annual interim reports to be submitted within 3 months of the yearly-cut off date for both the PMC on autoimmune diseases and the pregnancy registry.

GSK Response

GSK agrees to provide annual interim reports within 3 months of the yearly cut-off date for the phase IV PMC study on autoimmune diseases and the Cervarix US-based Pregnancy Registry.