

RECORD OF TELEPHONE CONVERSATION

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

Applicant:

GlaxoSmithKline Biologicals

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Telecon Summary:

Commitment to PMR

FDA Participants:

Non-FDA Participants:

Trans-BLA Group: No

Related STNs: None

Related PMCs: None

Telecon Body:

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Sent: Monday, September 21, 2009 10:48 AM

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Subject: Fw: Teleconference with FDA and GSK

Dear Lori and Michael,

As requested initially in the teleconference call on September 16, 2009, and then following further discussions with CBER on September 18, 2009, please find attached two documents. The first document includes the proposed wording for GSK's commitment with respect to the analytical epidemiological study and the second document contains the additional analyses on gestational ages of spontaneous abortions and the intervals between onset of pregnancy and abortion. Please note that the dataset for these analyses will be provided through our Firewall group in a follow-up mail as these datasets included unblinded information for ongoing studies. In the second document, there are also some early assessments on the study, including design and preliminary sample size calculations, and study initiation.

These documents will also be submitted to the Cervarix BLA.

Finally, please note for your records that I was not a participant at the teleconference on September 16 (see mail below) but I do remain a contact person for the Cervarix BLA.

Thank you and best regards,

Nicholas

Analytical Epidemiological Study To Assess The Risk Of Spontaneous Abortion

In teleconference call on September 16, 2009 and a subsequent call on September 18, 2009, CBER requested that GSK provide a commitment to conduct the study an analytical epidemiological study to assess the risk of spontaneous abortions with estimated timelines.

GSK response

GSK hereby commits to conduct an analytical epidemiological study to assess the risk of a first trimester spontaneous abortion in women whose estimated date of conception lies between day -30 until day +90 days from nearest vaccination. The final study design, which will include karyotyping in a subset to properly address the issue of background spontaneous abortions due to chromosomal abnormalities, will be completely and finally agreed by FDA. GSK commits to provide the draft protocol within 2 months of approval, the final protocol within 6 months of approval, and to initiate the study preferably within 6 months but no later than 12 months of protocol finalization.

Response to CBER request for further information on spontaneous abortions occurring in clinical trials with Cervarix

September 21, 2009

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Introduction

CBER has requested that GSK “provide further information on spontaneous abortions occurring in clinical trials. FDA requests all available data on the gestational ages of spontaneous abortions occurring within 90 days after administration of any *Cervarix* vaccination and of any controls, accompanied by a table or graph showing the intervals between onset of pregnancy and abortion.”

In teleconference call on September 16, 2009, CBER agreed with GSK’s proposal to provide a graph showing the interval between onset of pregnancy and spontaneous abortion for four different groups:

1. Women who became pregnant within 90 days after a *Cervarix* vaccination
2. Women who became pregnant more than 90 days after a *Cervarix* vaccination
3. Women who became pregnant within 90 days after a control vaccination
4. Women who became pregnant more than 90 days after a control vaccination

CBER also requested that GSK provide estimated time intervals between:

- Delivery of the final protocol for the post-marketing requirement study (analytical epidemiological study to assess the risk of spontaneous abortion) and the approval date for *Cervarix*.
- Initiation of the post-marketing requirement study (analytical epidemiological study to assess the risk of spontaneous abortion) and the approval date for *Cervarix*.

requested analyses of clinical data

This analysis included women from completed and ongoing trials of *Cervarix* (studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023) with a data lock-point (DLP) of August 31, 2008.

The analysis includes 19,871 subjects that received at least one dose of *Cervarix* and 17,548 subjects that received at least one dose of control.

Table 1 shows the total number of vaccinated subjects, number of pregnancies and number of pregnancies with spontaneous abortion reported up to August 31, 2008 for studies included in this analysis of pregnancy outcomes, by group.

Table 1 **Number of subjects vaccinated, reported pregnancies and reported pregnancies with spontaneous abortion outcome during the entire study period, by group (Total vaccinated cohort, data lock-point of August 31, 2008)**

	HPV	ALU	HAV360	HAV720	Pooled Control	Total
Number of subjects vaccinated	19,871	3,454	1,032	13,062	17,548	37,419
Number of reported pregnancies	3,696	380	10	3,190	3,580	7,276
Number of subjects reporting a spontaneous abortion	408	65	0	323	388	796

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)

ALU = Al(OH)₃ control group (Studies HPV-001, 003, 007, 015)

HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)

HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)

Pooled Control = ALU, HAV360 and HAV720 groups

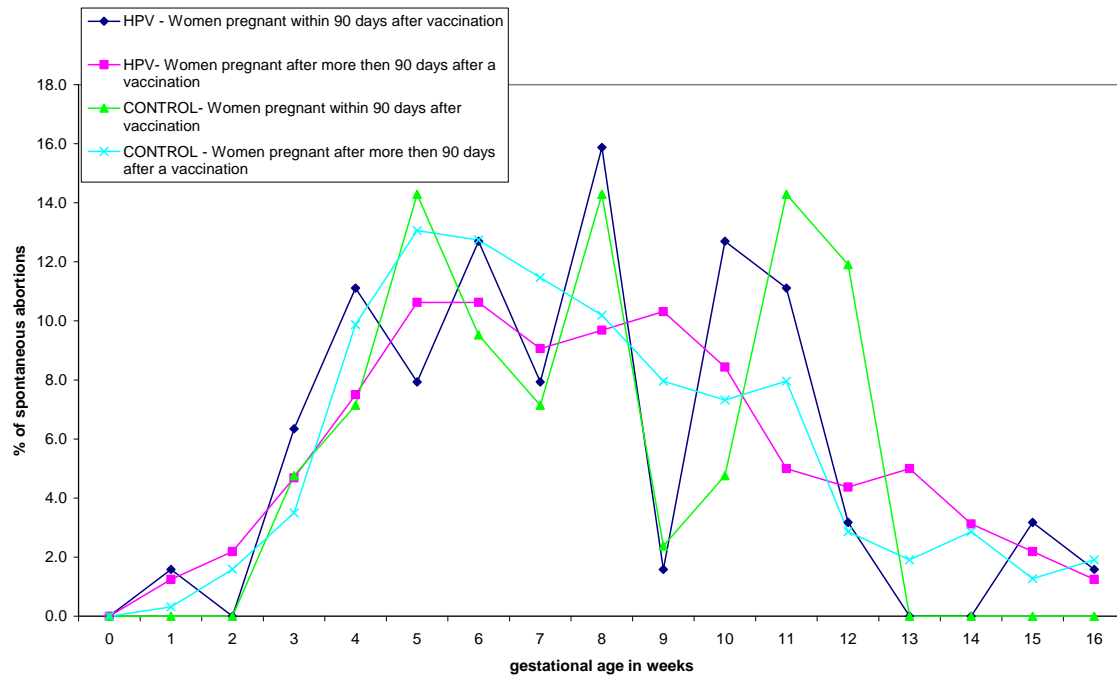
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]

The requested graph is shown in Figure 1. Please note that the following conventions have been followed to construct the graph:

- To determine the interval between pregnancy onset and vaccination: the interval was chosen based on the latest dose that precedes pregnancy onset. This is used to create subgroups of women pregnant within or after the 90 days post-vaccination.
- Pregnancy onset was estimated as last menstrual period (LMP) + 14 days
It should be noted that to date, in a few subjects, the reported LMP is still under query as the reported LMP date is not compatible with the reported outcome (the gestational age computed exceeds 20 weeks).
- Gestational age is defined as the interval between pregnancy onset and abortion.
- Women with missing data for their LMP were not included in this graph.

For clarity Figure 1 and Figure 2 are truncated. Overall figures are presented in Supplement 1 and Supplement 2.

Figure 1 Gestational ages of spontaneous abortions by treatment allocation and timing of pregnancy onset with respect to vaccination



The graph illustrates that the gestational age distribution is comparable in the HPV and control groups in women who became pregnant in the 90-day interval after vaccination and in women who became pregnant more than 90 days after vaccination.

To illustrate the interval between vaccination and the actual abortion, a graph of this interval is provided in Figure 2, for the same four groups shown in Figure 1. To determine the interval between abortion and vaccination, the interval was based on the latest dose that precedes pregnancy onset.

Figure 2 Interval between study vaccination and spontaneous abortion by treatment allocation and timing of pregnancy onset with respect to vaccination

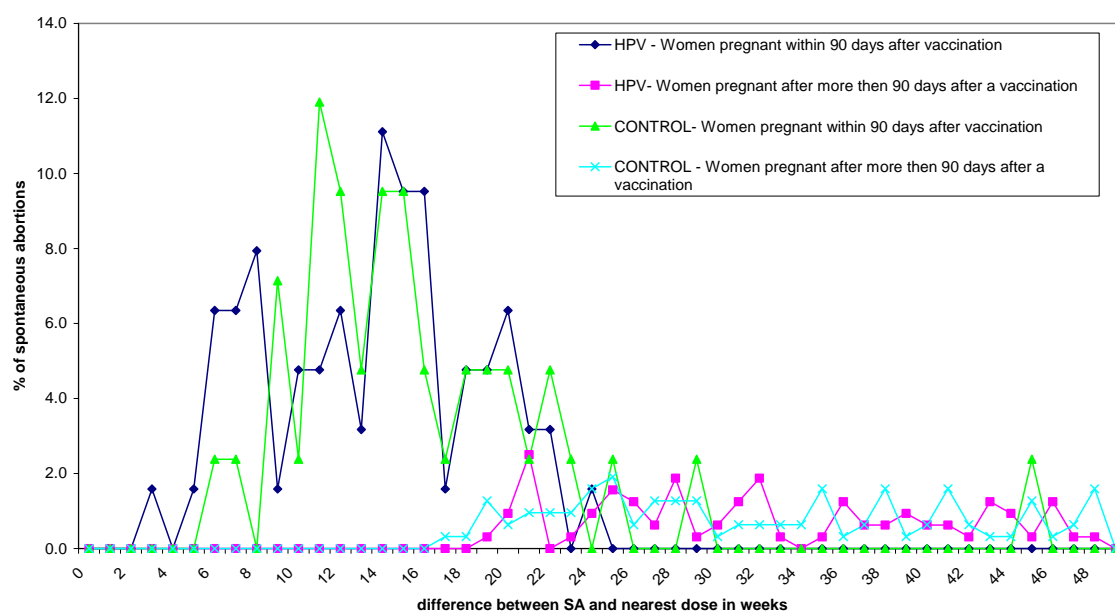


Figure 2 illustrates the following points:

- The interval between vaccination and time of abortion ranges from 2 to 26 weeks for the majority of reported spontaneous abortions.
- A significant proportion of the abortions in the group of women who became pregnant after vaccination in both groups (HPV and control) occur more than 90 days (14 weeks) after the last vaccination.
- Among women who became pregnant within 90 days of vaccination, there are no differences between the HPV and control group in the proportion of spontaneous abortions occurring at any given time point since vaccination.

Timelines for AN analytical epidemiological study to assess the risk of spontaneous abortion

GSK has reviewed the timelines for development of a protocol and study initiation. These timelines consider only what is currently foreseeable based on the initial assessment performed by GSK, within the limited time frame, as requested by CBER.

Since the timelines for study initiation are dependent on the size and complexity of the trial, we have performed a preliminary sample size assessment, which is provided in Appendix 1. These sample size estimates provide the required number of cases for a case-control study (defined as women who have a spontaneous abortion of a fetus, with a normal karyotype, of any gestational age less than 3 months) or the number of exposed women for a cohort design (defined as women who became pregnant within 90 days following a dose of *Cervarix*) and the number of person-years of follow-up needed in a

population of 15-25 year olds. These preliminary assessments suggest, for an observational study, in optimistic and conservative scenarios, the following sample sizes:

- 362 (optimistic scenario) or 7,973 (conservative scenario) cases derived from approximately 480,000 or 710,000,000 person-years, respectively (case-control design)
- 957 (optimistic scenario) or 6,676 (conservative scenario) exposed pregnant women derived from approximately 190,000 or 190,000,000 person-years respectively (cohort design)

These large sample sizes are largely driven by the need for karyotyping, which results in a 7 to 14-fold increase in the sample size estimate. As a result, it is expected that multiple sites will need to participate in the study, thus increasing the complexity of the protocol review and study set-up.

An additional complexity is that accrual of the required number of spontaneous abortions is expected to require several years and, over the same time period, the number of women in the targeted age range (15-25 years) who will be vaccinated in association with pregnancy onset is expected to significantly decrease, due to the fact that many cohorts of young women will have been vaccinated before initiating sexual activity (the target for universal HPV vaccination in most countries is pre-teenage girls). This consideration is currently not reflected in the above sample size estimates.

In addition, it is expected that this study may need to be conducted outside of the United States, as acknowledged by CBER, which may further increase the complexity of the protocol review and study set-up, as detailed below.

Development of full protocol

GSK has assessed the time required to develop a full protocol based upon the following considerations.

Identification of a study site(s) will be complex. The following list is considered a critical, but not exhaustive, list of elements to be present for a country or region to be considered for the proposed study:

1. Licensure and launch of *Cervarix* in candidate countries. This information is readily available to GSK.
2. Level of coverage of *Cervarix* in the 15-25 year old female population needed to conduct the study in candidate countries. This information requires availability of age-specific vaccine coverage rates. This is not readily available to GSK and cannot be derived from sales figures only.
3. Existence of referral clinics for adverse pregnancy outcomes in candidate countries meeting the above criteria. This information is not readily available to GSK and may require consultation with local experts in the field of reproductive health.
4. Cultural acceptability of karyotype testing in candidate countries. This information is not readily available to GSK and may require consultation with local experts in the field of reproductive health.

5. Technical know-how of karyotype testing in the referral clinics. This information is not readily available to GSK and may require consultation with local experts in the field of reproductive health.
6. Presence of investigative teams capable of undertaking the study. Since GSK Biologicals is not specialized in the area of reproductive health, this information is not readily available.
7. Following identification of potential study sites, it is likely that the investigators will not have collaborated previously with GSK and contractual agreement will need to be completed prior to further discussions on the protocol.

Following identification of a potential study site, finalization of the protocol is expected to require multiple rounds of review given the complexity of the study. This will help ensure the acceptability of the protocol for competent authorities/IRBs that will need to approve the study. In addition, it is expected that several rounds of review with CBER may also be required.

Study initiation

GSK has made a preliminary assessment of the time required to initiate the proposed study following finalization of the protocol considering the following points:

1. Ethics review is expected to be lengthy because of the inclusion of genetic testing.
2. Depending on the country (-ies) selected, the local approval time may be as lengthy as 6-12 months. In addition to the competent authorities, other review committees may need to approve the study because of the inclusion of genetic testing.
3. Study set-up is expected to be complex as the following elements will probably be required:
 - a. Training of investigators at study sites in conducting the interviews and collecting the necessary material for genetic testing
 - b. Standardization of the genetic testing and set-up of a quality control system
 - c. Communication to the local, regional and national health authorities on the importance of the study to avoid misunderstandings on the objective of the study with respect to genetic testing, which may affect immunization efforts.
 - d. Creation of tailored data collection tools. In the absence of prior experience in this type of study, GSK Biologicals will need to design new data collection tools.
 - e. Set-up of the information technology for data transfer. Since GSK Biologicals has not collaborated with the centers that may potentially perform the study, the study sites will have to be newly equipped.
4. It is expected that multiple centers and perhaps even multiple regions or countries may need to be involved in the study, given the large number of women to be monitored. This will require the set up of governing structures to ensure alignment between the sites.

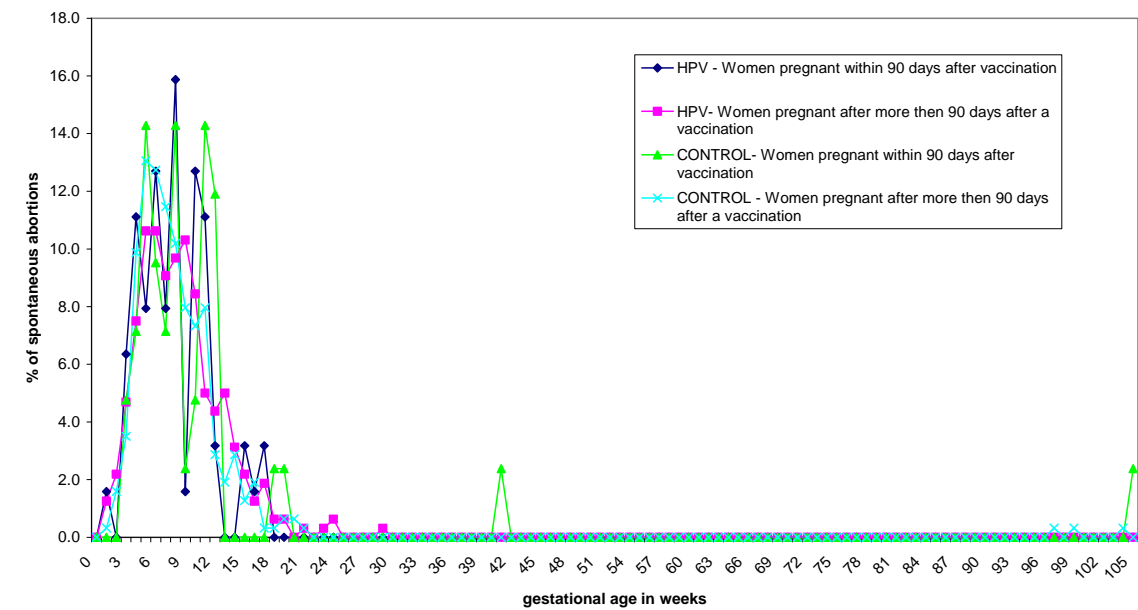
5. The study needs to be conducted simultaneously with actual vaccination of the target population because of its prospective nature. Study initiation is therefore contingent upon sufficient vaccination coverage within the study sites. As this is an observational study this is out of GSK's control.

Summary of the assessment

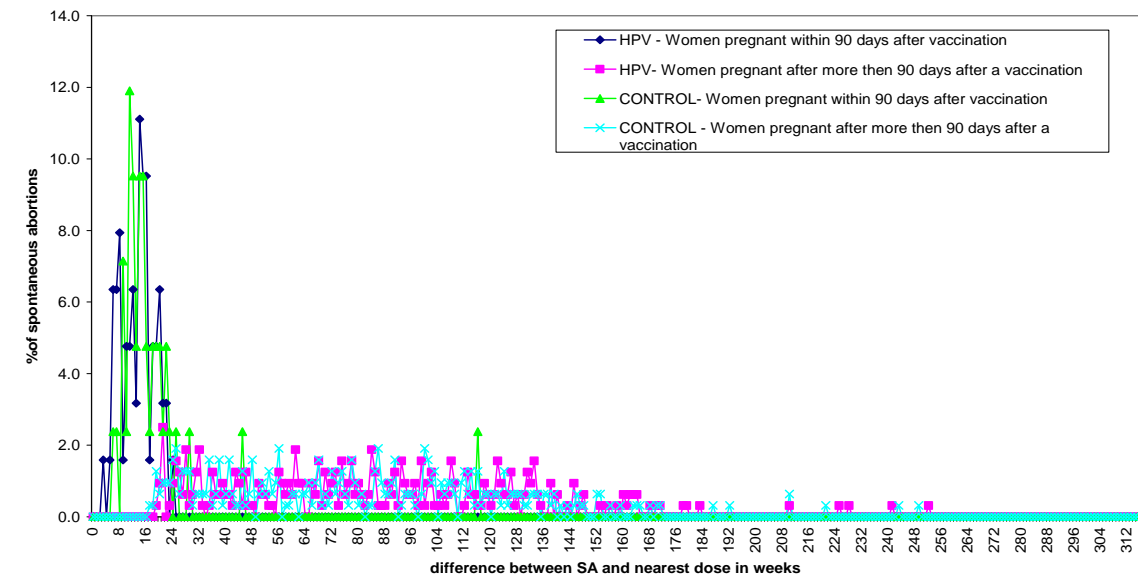
In conclusion, the size, nature and complexity of the required study mandate careful planning and set-up to ensure successful conduct. It is GSK's experience that epidemiological studies of a less complex nature can take up to 6 months to produce a final protocol and up to 12 months for study initiation from finalization of the study protocol. Nonetheless, GSK will make all necessary efforts to achieve delivery of the final protocol and study start for this complex trial within the timelines agreed with CBER. The CBER requested timelines are to provide the draft protocol within 2 months of approval, the final protocol within 6 months of approval, and to initiate the study preferably within 6 months but no later than 12 months of protocol finalization. Information regarding study design, sample size and projected timelines and the assumptions on which these elements rely contained in Sections 0 to 0 of the current document are based on an initial assessment performed by GSK within the timeframe requested by CBER. GSK will continue to work on these aspects with the objective of providing CBER with draft protocol and final protocol according to the above timelines. While this document identifies a number of potential complexities, there may be additional elements that GSK has not yet been able to identify within the limited timeframe available for this assessment. GSK is providing preliminary information concerning the study as envisioned by CBER within the time period given. GSK respectfully requests to continue close interactions with CBER throughout the study planning period in order to continually provide an update on the progress of planning activities as well as to discuss potential as yet unforeseen complexities that may be encountered.

SUPPLEMENTS

Supplement 1 Gestational ages of spontaneous abortions by treatment allocation and timing of pregnancy onset with respect to vaccination (full reporting period)



Supplement 2 Interval between study vaccination and spontaneous abortion by treatment allocation and timing of pregnancy onset with respect to vaccination (full reporting period)



APPENDIX 1 PRELIMINARY SAMPLE SIZE ASSESSMENT

The sample size was estimated for two potential designs, a case-control study and a cohort study. As self-controlled case series analysis was not considered as it is expected that a proportion of women will actively avoid pregnancy in the period post-vaccination and therefore the risk of the outcome (pregnancy leading to a spontaneous abortion) in the risk period is related to the exposure.

For both designs, two scenarios were assumed:

1. The conservative scenario in which the most conservative estimate for the expected range of each parameter is applied.
2. The optimistic scenario in which the most optimistic estimate for the expected range of each parameter is applied.

For each of these scenarios and for both designs the power was set at 80% for detecting a relative risk of a spontaneous abortion with normal karyotype of 2.0, using a two-sided test with alpha of 0.05.

Following identification of the needed sample size for each design, an estimation was made on the size of the population required to implement such a study.

Case-control design

A. Required number of cases

Cases would be women who had a spontaneous abortion of a fetus of any gestational age less than 3 months with a normal karyotype

Controls would be women with a pregnancy that developed beyond 20 weeks of gestation
Exposure is defined as a pregnancy that had its onset within 90 days after a dose of *Cervarix*.

The ratio of cases to controls is 1:4 in the optimistic scenario. This ratio is taken as the optimum ratio to maximize power while not jeopardizing the feasibility of the recruitment of the controls. In the conservative scenario, it is assumed that only 1 control can be recruited and matched to each case.

To estimate the expected exposure rate among cases and controls, the following parameters are taken into account:

1. Vaccination coverage. This was estimated to be 20% and 50 % for the conservative and optimistic scenarios, respectively. It is not expected that a higher coverage than 50% will be achieved in the 15-25 year olds.
2. Time since introduction of *Cervarix* in the target age population: since the risk window is considered as up to 90 days after a dose of vaccine, the likelihood of a pregnant woman having been exposed in the risk period is related to the time since the use of the vaccine in the target population. If the study were to be performed immediately after introduction of the vaccine, all vaccinated women presenting for an abortion would have been vaccinated recently. If the study takes place long after introduction of the vaccine, that proportion will be low. For the conservative scenario, this has been taken as 36 months, which is the sum of the time since first launch of *Cervarix* in Europe plus the time needed to initiate the

study. For the optimistic scenario, this has been taken as 24 months, assuming very rapid uptake of the vaccine in this age group.

3. The pregnancy avoidance behavior of women following vaccination. In the absence of data on the effect of the vaccine among pregnant women as well as the recommendation in approved prescribing information, it is likely, it is likely that women will be advised or will decide to avoid pregnancy immediately after vaccination. How long this avoidance will last is unclear. Preliminary data from potential investigators for the US Phase IV study suggest that the rate of pregnancy in the first 2 months after Gardasil vaccination is between a third and a tenth of the overall pregnancy rate in recipients of Gardasil, suggesting an avoidance rate of between 90% (conservative estimate) and 66% (optimistic estimate).

The exposure rate has thus been estimated as being:

The vaccination coverage \times (1 – the avoidance rate) \times the risk period/time since launch
The resulting exposure rate is thus estimated at 0.39%, and 4.96% for the conservative and optimistic scenarios, respectively.

The associated number of cases required is 7,973 and 362 for the conservative and optimistic scenarios, respectively.

(PASS 2005 Dupont W. 1988. "Power Calculations for Matched Case-Control Studies," Biometrics, Volume 44, pages 1157-1168)

B. Required population at risk size

To estimate the size of the population of 15 – 25 year old women within which such a case-control study could be performed, the following approach was followed:

First, the number of spontaneous abortions to be included to achieve the above number of cases of abortions with normal karyotype was estimated by taking the following elements into account:

1. The proportion of successful karyotype tests: not all women with spontaneous abortions undergo curettage and in some women no or insufficient material can be collected to do the testing. We assumed a 30% and 50% success rate for the conservative and optimistic scenarios, respectively.
2. The proportion of karyotypes that are normal among those successfully assessed. We assumed a 25% and 30% success rate for the conservative and optimistic scenarios, respectively.

The number of spontaneous abortions to be included in the analyses is thus estimated as

The number of spontaneous abortions / (the proportion of successful karyotypes \times the proportion of normal karyotypes)

The number of cases thus needed to be analyzed is 106,307 and 2,413 spontaneous abortions for the conservative and optimistic scenarios, respectively.

In the next step, the number of women entering the clinic for a spontaneous abortion that would need to be interviewed for study participation was estimated by estimating the participation rates. These were estimated to be 20% and 50% for the conservative and optimistic scenarios, respectively.

As a result, the number of women entering the clinic for a spontaneous abortion that would need to be interviewed for study participation was estimated to be 531,533 and 4,827 for the conservative and optimistic scenarios, respectively.

Finally, to estimate the population from which these women could be drawn, the following elements were taken into account:

1. Pregnancy yearly incidence rates: these were estimated to be 3% and 10% for the conservative and optimistic scenarios, respectively (Ventura 2008).
2. Rates of spontaneous abortions: these were estimated to be 5% (as observed for the control group in Study HPV 008 and 10% (Ventura 2008) for the conservative and optimistic scenarios, respectively. These rates reflect the fact that only abortions that are brought to medical attention will be included and that gestational age is limited to the first trimester.
3. The proportion of the general population served by the study clinics (capture rate): these were estimated to be 50% and 100% for the conservative and optimistic scenarios, respectively.

The required person-time among 15 -25 year old women has thus been estimated as being:

The number of women entering the clinic for a spontaneous abortion that would need to be interviewed for study participation / (the pregnancy yearly incidence rate x the spontaneous abortion rate x the capture rate)

As a result, the required person-time among 15-25 year old women was estimated to be approximately 710 million and 480,000 person-years for the conservative and optimistic scenarios, respectively.

Cohort design

A. Required cohort size

The exposed cohort is a cohort of women who became pregnant within 90 days following *Cervarix* vaccination.

The control cohort is a cohort of women who became pregnant later than 90 days after *Cervarix* vaccination or did not receive *Cervarix*.

The ratio of the exposed to the unexposed cohort was set at 1:1 for the conservative and 1:4 for the optimistic scenario. As for the case-control study, the 1:4 ratio is taken as the optimum ratio to ensure greater power while not jeopardizing the feasibility of the recruitment of the unexposed cohort. In the conservative case it is assumed that only 1 unexposed woman can be recruited and matched to an exposed woman.

The expected occurrence rate of the outcome (spontaneous abortion with normal karyotype) was estimated using the following parameters:

1. The proportion of successful karyotype tests: not all women with spontaneous abortions undergo curettage and in some women no or insufficient material can be collected to do the typing. We assumed a 30% and 50% success rate for the conservative and optimistic scenarios, respectively.
2. The proportion of karyotypes that are normal among those successfully assessed. We assumed a 25% and 30% success rate for the conservative and optimistic scenarios, respectively.
3. Rates of spontaneous abortions: these were estimated to be 5% (as observed for the control group in Study HPV 008 and 10% (Ventura, 2008) for the conservative and optimistic scenarios, respectively. These rates reflect the fact that only abortions that are brought to medical attention will be included and that gestational age is limited to the first trimester.

The expected incidence rate of the outcome of interest was thus estimated to be

The rate of spontaneous abortion x the proportion of successful karyotype tests x the proportion of karyotypes that are normal among those successfully assessed
As a result, the estimated incidence rate of the outcome of interest was thus estimated to be 0.4% and 1.5% for the conservative and optimistic scenarios, respectively.

The resulting sample size of the exposed cohort (women who became pregnant within 90 days of *Cervarix* vaccination) to detect a relative risk of 2.0 with 80% power is 6,676 and 957 for the conservative and optimistic scenarios, respectively.

(PASS 2005 Fisher's exact test for two independent proportions)

B. Required population at risk size

To estimate the size of the population of 15 – 25 year old women within which such a cohort study could be performed, the following approach was followed:

First, the number of pregnant women that would need to be interviewed for study participation was estimated by taking the following parameters into account:

1. Participation rates. These were estimated to be 20% and 50% for the conservative and optimistic scenarios, respectively.

2. Vaccination coverage. This was estimated to be 20% and 50 % for the conservative and optimistic scenarios, respectively. It is not expected that a higher coverage than 50% will be achieved in the 15-25 year olds.
3. The pregnancy avoidance behavior of women following vaccination. In the absence of data on the effect of the vaccine among pregnancy women, it is likely that women will be advised or will decide to avoid pregnancy immediately after vaccination. How long this avoidance will last is unclear. Preliminary data from potential investigators for the US Phase IV study suggest that the rate of pregnancy in the first 2 months after Gardasil vaccination is between a third and a tenth of the overall pregnancy rate in recipients of Gardasil, suggesting an avoidance rate of between 90% (taken as the conservative estimate) and 66% (optimistic estimate).

The number of pregnant women that would need to be interviewed for study participation was estimated to be

The required cohort size / (participation rate x vaccination coverage x (1 – avoidance behavior))

As a result, the number of pregnant women to be screened for study participation is estimated to be 1,669,000 and 11,259 for the conservative and optimistic scenarios, respectively.

Finally, to estimate the population from which these women could be drawn, the following elements were taken into account:

1. Pregnancy yearly incidence rates: these were estimated to be 3% and 10% for the conservative and optimistic scenarios, respectively (Ventura, 2008). These estimates result in pregnancy rates in the exposed period of 1.8% and 5.8% for the conservative and optimistic scenarios, respectively.
2. The proportion of the general population served by the study clinics (capture rate): these were estimated to be 50% and 100% for the conservative and optimistic scenarios, respectively.

The required person-time among 15 -25 year old women has thus been estimated as being:

The number of pregnant women to be screened for study participation / (the pregnancy yearly incidence rate x the capture rate).

As a result, the required person-time among 15 -25 year old women was estimated to be approximately 190 million and 190,000 for the conservative and optimistic scenarios, respectively.

The following table summarizes the above sample size estimations:

		Conservative scenario	Optimistic Scenario
Case - control	Cases required	7,973	362
	Controls required	7,973	1,448
	Approximate person years required (15 -25 yr old women)	710,000,000	480,000
Cohort	Exposed cohort size	6,676	957
	Unexposed cohort size	6,676	3,828
	Approximate person years required (15 -25 yr old women)	190,000,000	190,000

Practically, the person-year estimates mean that if the study were to be run in one year, a population of between 480,000 and 710 million women of 15 to 25 years old would be needed for a case-control study or between 190,000 and 190 million women of 15 to 25 years old for a cohort study. If the study would run longer, these numbers would need to be divided by the number of years the study were to run. It should be noted, however, that a longer study duration will affect the exposure rates (due to the expected impact of universal HPV vaccination of pre-teenage girls, see above) and can thus also increase the sample size.

It should be noted that the above estimates are the two (conservative and optimistic) extremes. It is more likely that the true estimate of the population of 15-25 year old women required for the study is in between these two extremes. Where the true estimate will lie is unpredictable at this stage and can only be assessed after identification of the study site(s) and feasibility assessment(s).