

Memorandum

Date November 22, 2009

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Subject BLA (STN 125259/0.43) Cervarix (Human Papillomavirus Vaccine, AS04 Adjuvant Adsorbed)
GlaxoSmithKline
- Response to the review team's comments on proposals for Class 2 Resubmission and HPV-008 Reporting and Analysis Plan (RAP) for efficacy

cc: Chron file
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Executive Summary

This amendment contains the applicant's responses to CBER's comments dated September 10, 2008 on the applicant's proposal dated July 29, 2008 describing the format and content of the HPV-008 final report and supplemental safety information to be provided as part of a Class 2 Resubmission.

In addition, a copy of the most recent HPV-008 Reporting and Analysis Plan (RAP) for efficacy (Amendment 2) is also provided. A copy of this RAP has also been submitted to IND -(b)(4)- (Amendment 673).

The applicant agrees to provide CBER with all analyses for HPV-008, including all analyses requested by CBER, in one submission at the time of the clock re-start.

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

Statistical Review

This review consists of two parts: Part 1. Review of the applicant's responses to the comments, and Part 2. Review of HPV-008 Reporting and Analysis Plan (RAP) for efficacy.

Part 1. Review of the applicant's responses to the comments

The applicant acknowledges CBER's comments and agrees to provide CBER with all analyses for HPV-008, including all analyses requested by CBER, in one submission at the time of the clock re-start.

Part 2. Review of HPV-008 Reporting and Analysis Plan (RAP) for efficacy

HPV-008, a pivotal study for this BLA, is an IND, Phase III, double-blind, randomized, controlled study to assess the efficacy of the HPV-16/18 vaccine in the prevention of CIN2+ lesions associated with HPV-16 or HPV-18 infection.

Objectives for Efficacy

Primary objective (Histopathological): To demonstrate efficacy of the candidate vaccine compared with control in the prevention of histopathologically confirmed **CIN2+ associated with HPV-16 or HPV-18** cervical infection detected within the lesional component of the cervical tissue specimen (by PCR). This objective will be assessed post dose 3 in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

Secondary objectives:

Virological

- To demonstrate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (12-month definition) with HPV-16 or HPV-18** (by PCR) post dose 3 in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- To evaluate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (6-month definition) with HPV-16 or HPV-18** (by PCR) post dose 3 in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- To evaluate efficacy of the candidate vaccine compared with control in the prevention of **persistent infection (6-month definition) with the following oncogenic HPV types:** HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR). This objective

will be assessed post dose 3 in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.

Histopathological

- To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically confirmed **CIN2+ associated with the following oncogenic HPV types** detected within the lesional component of the cervical tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
- To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically confirmed **CIN1+ associated with HPV-16 or HPV-18** detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
- To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically confirmed **CIN1+ associated with the following oncogenic HPV types** detected within the lesional component of the cervical tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Immunogenicity

- To evaluate immune correlates of protection against persistent infections (6- and 12-month definitions) with HPV-16 or HPV-18 and CIN2+ associated with HPV-16 or HPV-18 cervical infection (by PCR) post dose 3 using Month 7 and Month 24 immunogenicity evaluations.

Exploratory objectives: Twenty nine exploratory objectives including 10 objectives suggested by CBER. In addition, for all histopathological outcomes, an exploratory analysis referred to as “HPV type assignment algorithm” will be assessed. In this analysis, the association with HPV types will not only be based on the detection of HPV DNA in the lesion, but will also consider the presence of HPV types in the two immediately preceding cytology samples in case more than one HPV type was found in the lesion.

Endpoints for Efficacy

Primary endpoint: Histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA). **Note:** CIN2+ (cervical intraepithelial neoplasia) is defined as CIN2, CIN3, adenocarcinoma in-situ (AIS) and invasive cervical cancer.

Secondary endpoints:

Virological

- **Persistent** infection (12-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

- Persistent cervical HPV infection (12-month definition) is defined as the detection of the same HPV type (by PCR) at all available time points over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals).
 - **Algorithmic definition 1 of 12-month persistent infection:** A subject has a persistent infection for a specified HPV type (e.g., 16) if there exists a sequence of positive samples, not interrupted by negative samples, such that the total range is more than 10 months (> 300 days) apart and each two consecutive samples are no more than 14 months apart (≤ 420 days).
 - **Algorithmic definition 2 of 12-month persistent infection:** A subject with at least two positive samples (difference larger than 300 days) and no negative samples in between, that was not selected by algorithmic definition 1.
- Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).
 - Persistent cervical HPV infection (6-month definition) is defined as the detection of the same HPV type (by PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval (evaluations are planned at approximately 6-month intervals).
 - **Algorithmic definition of 6-month persistent infection:** There exists a sequence of positive samples, not interrupted by negative samples, such that the total range is more than 5 months (> 150 days) and each consecutive sample is no more than 10 months apart (≤ 300 days). In addition, all 12-month persistent infections will be considered as 6-month persistent infections.
 - **Persistent infection (6-month definition)** with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR).

Histopathological

- Histopathologically confirmed CIN2+ associated with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen (by PCR).
- Histopathologically confirmed CIN1+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA). **Note:** CIN1+ is defined as CIN1, CIN2, CIN3, adenocarcinoma in-situ (AIS) and invasive cervical.
- Histopathologically confirmed CIN1+ associated with the following oncogenic HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen.

Immunogenicity

- HPV-16 and HPV-18 ELISA titers and V5/J4 monoclonal antibody inhibition test titers and seroconversion will be assessed in vaccine recipients with breakthrough HPV-16 and/or HPV-18 infections and HPV-16 and/or HPV-18 associated neoplasias compared with selected non-cases (vaccine recipients without persistent infection or neoplasia matched for age, race and clinic site). These analyses will be restricted to subjects who are seronegative for the corresponding HPV type prior to vaccination.

Exploratory endpoints: Endpoints corresponding to all exploratory objectives are listed, including those that were suggested by CBER.

Statistical analysis overview for final and interim analysis

No stopping rules have been included in the HPV-008 interim and final analyses plan. Therefore, the study blind will be maintained **for the subjects remaining in the study** until completion of the 4-year follow-up (study end).

Type I error adjustment Plan for the interim analysis

The following plan was used to adjust alpha for the interim analysis.

1. For the primary endpoint and each secondary endpoint, a global alpha of 0.05 was used.
2. For the interim analysis, the applicant proposed to adjust alpha similar to the O'Brien-Fleming adjustment:
 - For the primary histopathological endpoint, the overall alpha of 0.05 will be split into 0.021 for the interim analysis and 0.039 for the final analysis.
 - For all the secondary endpoints, the overall alpha of 0.05 will be split into 0.021 for the interim analysis and 0.039 for the final analysis.
3. At the interim analysis, a sequential approach will be applied to control the Type I error.

The following table gives an overview of the interim and final analyses (see Appendix for exploratory endpoints). It specifies when the analyses are planned and which endpoints will be analyzed, together with the Type I error (α) that will be used for the confidence intervals and the lower limit that has to be reached for success.

Note that the final analysis will be done when:

- **at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 are detected and at least 15 cases of CIN2+ associated with HPV-18 are detected. This additional criterion provides at least 80% power to demonstrate efficacy, for the individual CIN2+ associated with HPV-18, with a 96.1 % lower limit above 0.**

OR

- at the end of the study when all subjects who didn't withdraw from the study completed the Month 48 visit. When the final analysis is done before the end of the study, the analysis will be

performed by an external statistician to maintain the blinding. An additional analysis will be performed at the end of the trial and will be reported in an annex report.

Table. Statistical analysis overview

	Interim		Final	
Timing	• 23 cases of CIN2+ associated with HPV-16 or HPV-18 after Month 0 visit		• <i>At least 36 cases of CIN2+ associated with HPV-16 or HPV-18 and at least 15 cases of CIN2+ associated with HPV-18</i> OR • All subjects who didn't withdraw from the study completed the Month 48 visit	
Primary endpoint				
	Interim		Final	
		Histopathological		Histopathological
		CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial serostatus ²		CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial serostatus ²
Alpha		0.021		0.039
LL of CI		> 0%		> 30%
Secondary endpoints				
	Interim		Final	
	Virological	Histopathological	Virological	Histopathological
	Persistent infection (12-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus ² , LL>0%	CIN2+ associated with oncogenic types ¹ detected within the lesional component of the cervical tissue specimen (by PCR), LL>0%	Persistent infection (12-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus ² , LL>50%	CIN2+ associated with oncogenic types ¹ detected within the lesional component of the cervical tissue specimen (by PCR), LL>15%
	Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus ² , LL>0%	CIN1+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial serostatus ² , LL>0%	Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus ² , LL>50%	CIN1+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR), overall and stratified according to initial serostatus ² , LL>30%
	Persistent infection (6-month definition) with oncogenic types ¹ (by PCR), LL>0%	CIN1+ associated with oncogenic types ¹ detected within the lesional component of the cervical tissue specimen (by PCR), LL>0%	Persistent infection (6-month definition) with oncogenic types ¹ (by PCR), LL>15%	CIN1+ associated with oncogenic types ¹ detected within the lesional component of the cervical tissue specimen (by PCR), LL>10%
Alpha	0.021	0.021	0.039	0.039

Study Cohorts

Study cohorts for interim analysis

- **Total vaccinated cohort for efficacy at interim analysis 1 (TVC-1):** The Total vaccinated cohort for efficacy at the interim analysis 1 will include all vaccinated subjects (at least one dose) for whom data concerning efficacy endpoint measures are available and have a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. For this cohort, the follow-up time for a subject will start at the day after Dose 1. Subjects will be classified according to the randomized treatment assignment. For all stratified efficacy endpoints, the principal analysis will be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. At the interim analysis, the TVC-1 will be the primary cohort for all endpoints.
- **Total vaccinated cohort for efficacy at interim analysis 2 (TVC-2):** The Total vaccinated cohort for efficacy at the interim analysis 2 will include all vaccinated subjects (at least one dose) for whom data concerning efficacy endpoint measures are available and have a normal cytology (negative or ASC-US/oncogenic HPV negative by HCII) at Month 0. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for a subject will start at the day after Dose 1. Subjects will be classified according to the randomized treatment assignment. For all stratified efficacy endpoints, the principal analysis will be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. This analysis will complement the analysis on TVC-1 and will only be performed on the primary and secondary endpoints that are associated with HPV-16 and/or HPV-18.
- **According-To-Protocol (ATP) cohort for efficacy at interim analysis:** The ATP cohort for efficacy at interim analysis will include all subjects who received three doses of the study vaccine (HPV or HAV), for whom data concerning efficacy endpoint measures are available and have a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 and Month 6 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). For all stratified efficacy endpoints, the principal analysis will be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. For this cohort, the follow-up time for a subject will start at the day after Dose 3.

Study cohorts for final analysis

- **According-To-Protocol cohort for analysis of efficacy (ATP):** The ATP cohort for analysis of efficacy will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination violations), for whom data concerning efficacy endpoint measures are available and have a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 and Month 6 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for a subject will start at the day after Dose 3. **At the final analysis, the ATP cohort for efficacy will be the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA positive women at Month 0.**
- **According-To-Protocol (ATP) cohort in oncogenic HPV “naïve” woman for analysis of efficacy (ATP-naïve):** The ATP cohort for analysis of efficacy in oncogenic HPV naïve woman will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination violations), for whom data concerning efficacy endpoint measures are available and have a normal (negative or ASC-US/oncogenic HPV negative by HCII) cytology at Month 0. In addition, subjects should be negative for all High Risk HPV type (by DNA) at Month 0, seronegative (by ELISA) at Month 0 for both HPV-16 and HPV-18 and HPV DNA (by PCR) at Month 6 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for a subject will start at the day after Dose 3. Subjects will be classified according to the randomized treatment assignment. This analysis will supplement the overall ATP analysis and will only be performed on the primary, secondary and selected exploratory endpoints.
- **Total vaccinated cohort:** This cohort will include all vaccinated subjects for whom data are available. Thus, the Total vaccinated cohort analysis will include all subjects with at least one vaccine administration documented. It will be performed per treatment actually administered.
- **Total vaccinated cohort for efficacy 1 (TVC-1):** The Total vaccinated cohort for efficacy will include all vaccinated subjects (at least one dose) for whom data concerning efficacy endpoint measures are available and have a normal or low-grade cytology (negative or ASC-US or LSIL) at Month 0. The Total vaccinated cohort analysis will be performed per treatment actually administered. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint), except for the endpoints evaluated in HPV DNA positive women at Month 0. For this cohort, the follow-up time for a subject will start at the day after Dose 1. At the final analysis, the Total vaccinated cohort for efficacy will be the primary cohort for all endpoints evaluated in HPV DNA positive women at Month 0.
- **Total vaccinated cohort for efficacy 2 (TVC-2):** This cohort will include all vaccinated subjects (at least one dose) for whom data concerning efficacy endpoint measures are

available and who have a normal cytology (negative or ASCUS/oncogenic HPV negative by HCII) at Month 0. In addition, subjects should be negative for HPV DNA (by PCR) at Month 0 for the corresponding HPV type in the analysis (i.e., HPV type associated with the efficacy endpoint). For this cohort, the follow-up time for a subject will start at the day after Dose 1. Subjects will be classified according to the randomized treatment assignment. For all stratified efficacy endpoints, the principal analysis will be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. This analysis will complement the analysis on TVC-1 and will only be performed on the primary, secondary endpoints and some important exploratory endpoints.

- **Total vaccinated cohort for efficacy in oncogenic HPV “naïve” woman (TVC-naïve):**
This cohort will include all vaccinated subjects (at least one dose) for whom data concerning efficacy endpoint measures are available and who have a normal cytology (negative or ASC-US/oncogenic HPV negative by HCII) at Month 0. In addition, subjects should be seronegative (by ELISA) for both HPV-16 and HPV-18 and negative for all High Risk HPV DNA (by PCR) at Month 0. For this cohort, the follow-up time for a subject will start at the day after Dose 1. Subjects will be classified according to the randomized treatment assignment. This analysis will supplement the analysis of the overall TVC-1 and TVC-2 cohorts and will only be performed on the primary, secondary and selected exploratory endpoints.

Statistical Methods

Primary analysis: Vaccine efficacy using conditional exact method

The vaccine efficacy (VE) for all endpoints will be calculated using a conditional exact method. This method computes an exact confidence interval (CI) around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the follow-up time of the subjects within each group. VE is then defined as 1 minus the rate ratio.

The follow-up time for each subject will start:

- at the day after first vaccination (Month 0) if analyses are done on the Total vaccinated cohort for efficacy, or
- at the day after third vaccination (Month 6) if analyses are done on the ATP cohort for efficacy.

The follow-up time for each subject will end:

- at the time of the event (e.g., the start of the persistent infection or the time of the histopathological endpoint)
- at Month 48 for subjects who completed the study and did not have an event or
- at the latest visit for which data is available for subjects who did not yet completed the study at the time of the interim analysis or final analysis (if 36 CIN2+ cases have been reached before all subjects did their Month 48 visit) and did not have an event:

- For histopathological endpoints, we take the date of the last biopsy or last cytology (result satisfactory or satisfactory without endocervical component), whichever comes latest,
- For cytological endpoints, we take the date of the last cytology (result satisfactory or satisfactory without endocervical component),
- For (persistent) infection endpoints, we take the date of the last cervical sample where lab results are available.

Further note that for the analysis of 6-month persistent infection, only subjects with at least 5 months follow-up after the Month 6 visit (Total vaccinated cohort) or after the Month 12 visit (ATP cohort) will be included. For the analysis of 12-month persistent infection, only subjects with at least 10 months follow-up after the Month 6 visit (Total vaccinated cohort) or after the Month 12 visit (ATP cohort) are included.

The follow-up time will be calculated in days as Date of end of follow-up period – Date of vaccination, and expressed in person-years at risk (number of days/365.25).

Confirmatory analyses

The following confirmatory analyses will only be performed at the final analysis.

Vaccine efficacy using Cox regression models

In addition to the primary analysis, VE and its CI will also be calculated using a Cox regression model. This methodology can take into account the specific risk factors which might have been imbalanced, by chance, at the beginning of the trial between the vaccinated and control group. Risk factors that will be investigated include age, country, and other risk factors (The covariates used in the Cox regression are specified in Section 5.2.3 Adjustment for covariates in Cox regression model). VE is then calculated as 1 minus the hazard ratio. Kaplan-Meier curves for both groups will also be shown and compared using the Log-rank test. Cox regression assumes proportional hazards throughout the follow-up period. This assumption will be checked by a test based on the Schoenfeld residuals. If there is strong evidence that the hazard is not constant over the surveillance period, then alternative approaches to analyze the data will be examined according to the following:

- Cox regression models with time varying covariates, using fractional polynomials to identify the function of the time that best fits. The following functions of the time will be explored: -2, -1, -1/2, log, identity, 1/2, 2, 3
- Piecewise Cox regression model, partitioning the surveillance period in three periods based on equal numbers of events.
- In both situations, the Akaike's Information Criterion (AIC) and the Schwarz Bayesian Criterion (SBC) will be calculated.

Vaccine efficacy using an unconditional asymptotic method

At the end of the trial, VE will also be calculated using attack rates and using only subjects that completed the study (i.e., had a Month 48 visit). This will be done using the asymptotic version of a method proposed by Chan and Zhang (1999).

Summary of immune correlates of protection

HPV-16 and HPV-18 ELISA titers, V5/J4 monoclonal antibody inhibition test **and pseudovirion** titers and seroconversion will be assessed in vaccine recipients with breakthrough HPV-16 and/or HPV-18 persistent infections and HPV-16 and/or HPV-18 associated neoplasias compared with selected non-cases (vaccine recipients without persistent infection or neoplasia matched for age, race and clinic site). These analyses will be restricted to subjects who are seronegative for the corresponding HPV type prior to vaccination.

For persistent infection and CIN2+ associated with HPV-16 (HPV-18), Cox regression models with the following covariates will be presented:

- the log10 of the anti-HPV-16 (anti-HPV-18) antibody titer at Month 7
- the log10 V5 (J4) monoclonal antibody titer at Month 7
- **the log10 of the pseudovirion anti-HPV-16 (anti-HPV-18) antibody titer at Month 7**
- the seroconversion status of a subject for the anti-HPV-16 (anti-HPV-18) antibody titer
- the seroconversion status of a subject for the V5 (J4) monoclonal antibody titer
- **the seroconversion status of a subject for the pseudovirion anti-HPV-16 (anti-HPV-18) antibody titer**

The hazard ratio per ten-fold increase in the value of anti-HPV-16 (anti-HPV-18) or V5 (J4) monoclonal antibody will be presented, together with the hazard ratio of responders (subjects who seroconvert) versus non-responders (subjects who don't seroconvert). Titers less than the cutoff will be given an arbitrary value of half of the cutoff.

Reviewer's comment: Given that the number of breakthrough cases will not be large, too many covariates presented in the Cox regression models may cause over-adjustment. In addition, collinearity between covariates may emerge.

Comments and Questions to Sponsor:

- There are more than 30 exploratory objectives to be evaluated. In these analyses, Type I errors are not adjusted for multiple comparisons. Please acknowledge that results based on these analyses cannot be used to support future supplements for labeling changes.
- (Page 38, Section 4.5.3) Given that the number of breakthrough cases will not be large, too many covariates presented in the Cox regression models may cause over-adjustment. In addition, collinearity between covariates may emerge. Please comment.
- (Minor editing on Page 13): Please add "HRW (=High-risk (oncogenic) HPV types without HPV-16 or HPV-18: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)" in the fourth paragraph.

Appendix

Exploratory endpoints				
	Interim		Final	
	Virological	Histopathological	Virological	Histopathological
	<p>Clearance of HPV-16 or HPV-18 (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 at Month 0, overall and stratified according to initial serostatus².</p> <p>Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR) in women with a history of infection with the other vaccine type (seropositive and/or DNA positive) prior to vaccination and with a normal or low-grade cytology at Month 0</p> <p>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) in subjects with only 2 doses of the study vaccine.</p>	<p>Any cytological abnormality associated with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus².</p> <p>Any cytological abnormality associated with oncogenic¹ types (by PCR).</p> <p>Any cytological abnormality, CIN1+ and CIN2+, irrespective of HPV DNA results</p> <p>CIN2+ associated with HPV-16 or HPV-18 cervical infection (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</p> <p>VIN1+ or VAIN1+ (combined endpoint) associated with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus².</p> <p>VIN1+ or VAIN1+ (combined endpoint) associated with oncogenic types¹</p> <p>VIN1+ or VAIN1+ (combined endpoint), irrespective of HPV DNA results found in the lesional component of the tissue specimen.</p>	<p>Clearance of HPV-16 or HPV-18 (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 at Month 0, overall and stratified according to initial serostatus².</p> <p>Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR) in women with a history of infection with the other vaccine type (seropositive and/or DNA positive) prior to vaccination and with a normal or low-grade cytology at Month 0.</p> <p>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) in subjects with only 2 doses of the study vaccine.</p> <p>Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA) in subjects with only 2 doses of the study vaccine.</p>	<p>CIN2+ associated with 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 serostatus².</p> <p>Any cytological abnormality associated with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus².</p> <p>Any cytological abnormality associated with oncogenic¹ types (by PCR).</p> <p>Any cytological abnormality, CIN1+ and CIN2+, irrespective of HPV DNA results</p> <p>CIN2+ associated with HPV-16 or HPV-18 cervical infection (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</p> <p>VIN1+ or VAIN1+ (combined endpoint) associated with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial serostatus².</p> <p>VIN1+ or VAIN1+ (combined endpoint) associated with oncogenic types¹</p> <p>VIN1+ or VAIN1+ (combined endpoint), irrespective of HPV DNA results found in the lesional component of the tissue specimen.</p>

	Exploratory endpoints			
	Interim		Final	
	Virological	Histopathological	Virological	Histopathological
	Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA) in subjects with only 2 doses of the study vaccine.	Administration of local cervical therapy (LEEP, CONE, KNIFE or LASER), irrespective of baseline HPV DNA status.	<i>Persistent infection (6 and 12-month definition) with subgroup of oncogenic types¹ (by PCR)</i>	cervical therapy (LEEP, CONE, KNIFE or LASER), irrespective of baseline HPV DNA status. Administration of local <i>HPV-type assignment for CIN1+ and CIN2+ endpoints</i>
Alpha	0.021	0.021	0.039	0.039

Oncogenic types: HPV-16,18,31,33,35,39,45,51,52,56,58,59,66 and 68

Overall and stratified according to initial serostatus: The analysis will be done for subjects seronegative at baseline (Month 0) for the corresponding HPV type (principal analysis), for all subjects and for subjects seropositive at baseline (Month 0) for the corresponding HPV type.