

## Statistical Review and Evaluation

**Date** November 30, 2009

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**Subject** STN: BL 125259/0 – Resubmission  
Cervarix (Human Papillomavirus Vaccine, AS04 Adjuvant Adsorbed)  
GlaxoSmithKline Biologicals

**cc:** Chron file  
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### Executive Summary

STN: BL 125259 for *Cervarix* (Human Papillomavirus [Types 16 and 18] Monophosphoryl Lipid A Vaccine, Adsorbed) was originally filed to CBER on March 29, 2007. On December 14, 2007, CBER issued a Complete Response (CR) letter to the applicant, GlaxoSmithKline (GSK). GSK had provided the responses through the first half of 2008 in satisfaction of the CR letter. On March 30, 2009, a Class 2 resubmission was completed and the review clock was re-started.

The proposed indication for Cervarix is the prevention of cervical cancer (squamous cell cancer and adenocarcinoma) in females of 10 to 25 years of age by protecting against the following precursor lesions and infections caused by oncogenic HPV types 16 and 18: CIN2 and CIN3, CIN1, abnormal cytology (i.e., ASC-US, LSIL and HSIL), persistent infection, and incident infection.

The pivotal study HPV-008 showed that:

1. the primary endpoint of the study, prevention of CIN2+ lesions associated with HPV-16 and/or HPV-18 (HPV-16/18), was met with a high level of vaccine efficacy (92.9%)

[79.9, 98.3],  $p < 0.0001$ ) in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6.

2. All other histopathological (CIN3+, CIN1+, ASC-US+ and VIN/VaIN1+) were statistically significant in the ATP cohort for efficacy.
3. The virological (incident, 6-month and 12-month persistent infection) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy; however, the clinical meaningfulness of these findings needs to be assessed by the clinical reviewer, Dr. Nancy Miller.
4. As to the findings that the candidate vaccine reduced persistent infection and precancerous lesions or AIS caused by oncogenic HPV types other than HPV-16 and HPV-18, HPV-31 may be the only one reached statistical significance if an adequate Type I error adjustment had been performed. The clinical meaningfulness of these findings is subject to the clinical reviewer's judgment.

Based on the results of HPV-008, the proposed indication for Cervarix is the prevention of cervical cancer (squamous cell cancer and adenocarcinoma) in females of 10 to 25 years of age by protecting against the following precursor lesions and infections caused by oncogenic HPV types 16 and 18: CIN2 and CIN3, CIN1 may be granted.

In Study HPV-008, the clinical relevance of the unbalanced incidence rates of spontaneous abortion between the vaccine and the control groups should be determined by the clinical reviewer, Dr. Nancy Miller.

As requested by the Chair of this BLA review committee, the statistical reviewer made the following table to list the items in the FDA CR letter (dated December 14, 2007) she has reviewed.

CR Item No.	EDR Sequence No.	Amendment No.	Section Number
2c(i)	0036	0.37	V.3 Safety
3	0036	0.37	V.2 Efficacy
4	0029	0.30	V.2 Efficacy
5	0029	0.30	V.2 Efficacy
6a	0029	0.30	V.2 Efficacy
6b	0029	0.30	V.2 Efficacy
6c	0029	0.30	V.2 Efficacy
7	0029	0.30	V.2 Efficacy
8	0029	0.30	V.2 Efficacy
9	0029	0.30	V.2 Efficacy
10	0029	0.30	V.2 Efficacy
11	0029	0.30	V.2 Efficacy

The applicant's responses to most items appear to be acceptable.

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## **I. BACKGROUND**

This Biologics License Application (STN BL 125259/0) was submitted on March 29, 2007 by GlaxoSmithKline (GSK) for Cervarix (Human Papillomavirus [Types 16 and 18] Monophosphoryl Lipid A, Recombinant). The clinical development of this vaccine in the United States has been investigated under BB-IND -(b)(4)-, initially submitted to CBER on September 08, 1998.

The proposed indication for Cervarix is in females 10 through 25 years of age for the prevention of cervical cancer (squamous cell cancer and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions and infections caused by oncogenic human papillomavirus (HPV), including types 16 and 18 and some non-vaccine types:

- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 or cervical adenocarcinoma *in situ* (AIS),
- cervical intraepithelial neoplasia (CIN) grade 1,
- abnormal cytology (i.e., atypical squamous cells of undetermined significance [ASC-US], low- and high-grade squamous intraepithelial lesions [LSIL and HSIL]),
- persistent infection, and
- incident infection.

In a Complete Response (CR) letter dated December 14, 2007, CBER requested the applicant for additional information regarding efficacy, safety, pharmacovigilance, CMC, and assays. In response to CBER's CR letter, GSK had provided a series of amendments. On March 30, 2009, a Class 2 resubmission was completed and the review clock was re-started.

This statistical review is mainly organized into two categories: 1) the reported pivotal studies (HPV-008 and HPV-007), and 2) the applicant's responses to the items in CR letter that focus on the issues of efficacy and safety. For the pivotal studies, the review focuses on study design, statistical analysis, and study results for efficacy, immunogenicity, and safety evaluations.

## **II. STATISTICAL REVIEW OF EFFICACY**

### **II.1 Introduction**

The pivotal study for efficacy of the HPV-16/18 vaccine is the Phase III Study HPV-008, which is supplemented by Phase IIb efficacy data from Study HPV-007, a continuation of Study HPV-001. The final analysis reports HPV-008 and HPV-007 (36 Months) are included in the resubmission.

#### HPV Infection Definitions

The following definitions were used for the efficacy data presented in the BLA:

- **Incident infection:** First detection of a specific HPV type (by PCR) in a subject previously negative for that HPV type; incident infections could be transient or become persistent.
- **Persistent infection** (6-month definition): Detection of the same HPV type (by PCR) in cervical samples over a minimum period of approximately 6 months with no negative samples in between.
- **Persistent infection** (12-month definition): Detection of the same HPV type (by PCR) at all available timepoints over a minimum of approximately 12 months with no negative samples in between.

## II.2 Study HPV-008

### Study Design

Study HPV-008 is an IND Phase III, double-blind, randomized, controlled study to evaluate the **efficacy** of the HPV-16/18 vaccine in the prevention of CIN2+ lesions associated with HPV-16 or HPV-18 infection in healthy adolescent and young adult women 15-25 years of age.

A total of 18729 women aged 15 to 25 years from Asia Pacific, Europe, Latin America and North America were randomized (1:1) into two treatment groups: 1) HPV group: HPV-16/18 L1 VLP AS04 vaccine, and 2) HAV group: Hepatitis A vaccine (*Havrix*-based investigational formulation). Study subjects were supposed to receive three doses of vaccine or control according to a 0, 1, 6-month schedule. Approximately a follow-up period of 48 months was planned for all subjects.

### Primary Objective

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 was assessed post Dose 3 in adolescent and young adult women who were 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). The principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample.

### 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 18 serostatus (by ELISA).

CIN2+ was defined as CIN2, CIN3, adenocarcinoma in-situ (AIS) or invasive cervical cancer.

### 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 were 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 18 (by PCR) post Dose 3 in adolescent and young adult women who were 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 was assessed post Dose 3 in adolescent and young adult women who were negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.

### 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 18 serostatus (by ELISA).  
Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type (by PCR) at all available timepoints over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals).
- Persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).  
Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type (by PCR) in cervical samples at two consecutive evaluations over approximately a 6-month interval.
- 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).

### Secondary objectives (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 (or combination of 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 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 (or combination of 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.

#### Secondary endpoints (Histopathological)

- Histopathologically-confirmed CIN2+ associated with the following oncogenic HPV types (or combination of 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.
- 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 18 serostatus (by ELISA).  
CIN1+ was defined as CIN1, CIN2, CIN3, AIS or invasive cervical cancer.
- Histopathologically-confirmed CIN1+ associated with the following oncogenic HPV types (or combination of 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.

#### Analysis Cohorts

Six study cohorts were considered for analysis of efficacy. [Table 1](#) illustrates the definition of all study cohorts.

**Table 1 Description of study cohorts**

	<b>ATP</b>	<b>TVC-1</b>	<b>TVC-2</b>	<b>TVC</b>	<b>ATP-naïve</b>	<b>TVC-naïve</b>
Number of doses vaccinated	3	≥ 1	≥ 1	≥ 1	3	≥ 1
Complying with the procedures defined in the protocol	✓				✓	
Data concerning efficacy endpoint measures were available	✓	✓	✓	✓	✓	✓
cytology at Month 0	normal or low-grade	normal or low-grade	normal		normal	normal
Negative HPV DNA (by PCR) at Months 0 (corresponding HPV type)	✓	✓	✓		✓	✓

Negative HPV DNA (by PCR) at Months 0 (all other high risk HPV types)					✓	✓
Seronegative (by ELISA) at Month 0 for both HPV-16 and HPV-18					✓	✓
Negative HPV DNA (by PCR) at Months 6 (corresponding HPV type)	✓				✓	
Follow-up time started at the day after	Dose 3	Dose 1	Dose 1	Dose 1	Dose 3	Dose 1

**Reviewer's comments:** I constructed Table 1 based on the information described in the HPV-008 final report.

At the final analysis, the ATP cohort for efficacy was the primary cohort for all endpoints, except for endpoints evaluated in HPV DNA positive women at Month 0.

### Study Analyses

- An event-driven interim analysis was performed when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the Total Vaccinated cohort for efficacy 1 (TVC-1). The efficacy objectives were assessed at the interim analysis post Dose 1 in adolescent and young adult women who were DNA negative for the corresponding HPV type at Month 0. Data from this interim analysis were reported in a separate interim clinical study report dated March 2007.
- An event-driven final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. The efficacy objectives were assessed at the final analysis post Dose 3 in women who were **DNA negative for the corresponding HPV type at Months 0 and 6**. These data are presented in this final clinical study report. The endpoints assessed at the interim analysis were assessed again at the final analysis with higher power to evaluate the endpoints and adjustment of the alpha for the two analyses.

### Final Analysis of Efficacy

An event-driven final analysis of all histopathological and virological endpoints was performed when at least 36 evaluable cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection. The primary analysis of efficacy was performed on the ATP cohort for efficacy. Vaccine efficacy in the prevention of CIN2+ associated with HPV-16 or HPV-18 infection, and its 96.1% confidence interval (CI), was calculated. If the lower limit of this CI was above 30%, the primary histopathological endpoint was met.

Additional efficacy analyses were performed on the Total Vaccinated cohort for efficacy 1 (TVC-1) and using the “HPV type assignment” algorithm (exploratory analysis). Results of the primary, secondary and exploratory efficacy endpoints are presented in this final clinical study report along with the safety and immunogenicity results up to the DLP. As the study is ongoing at the time of this final event-driven analysis, an additional descriptive summary of results will be presented in a separate annex report when all subjects have completed all study activities (Month 48). The endpoints assessed at the interim analysis were assessed again at the final analysis with higher power to evaluate the endpoints, and adjustment of the alpha for the two analyses.

Calculation of the sample size of the study was based on the assumption of 5% HPV-16 and HPV-18 DNA positive subjects and a drop-out rate of 35%. The power at final analysis was above 91% to assess all primary and secondary efficacy endpoints, except CIN2+ associated with oncogenic HPV types which had a power of 62%.

The vaccine efficacy (VE) for all endpoints was calculated using a conditional exact method (primary analysis). This method computes an exact CI around the rate ratio (ratio of the event rates in the HPV group versus the HAV 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 and p-values are calculated using the Fisher’s exact test to compare the attack rates between both groups. In addition, confirmatory analyses were performed which considered the effect of age and region on the estimate of the efficacy using a Cox regression model. At the end of the study (Month 48) other confirmatory analyses will be performed, such as the unconditional asymptotic method.

A further analysis of the HPV-008 study data using the HPV type assignment algorithm (TAA) was performed. In this exploratory analysis, the association with HPV-16/18 was based not only on the detection of HPV DNA in the lesion, but also evaluated the presence of HPV types in the two immediately preceding cytology samples when more than one HPV type was found in the lesion.

## **Study Results**

### **Results of primary endpoint**

There were 60 cases of the primary endpoint (CIN2+ associated with HPV-16 and/or HPV-18 [HPV-16/18]) detected in the ATP cohort for efficacy (4 in the HPV group and 56 in the HAV group), 12 of which were cases of CIN3+ (2 in the HPV group and 10 in the HAV group). The vaccine efficacy for the primary endpoint was high and statistically significant (VE= 92.9% [79.9, 98.3],  $p<0.0001$ , [Table 2](#) (Synopsis Table 1 in the Clinical Study Report for HPV-008)) in HPV DNA negative and seronegative subjects. In addition, statistically significant vaccine efficacy was observed for both HPV-16 and HPV-18 with point estimates of 95.7% for HPV-16 and 86.7% for HPV-18. In TVC-1, where vaccine efficacy was assessed from the administration of the first vaccine dose, there were 96 cases of the primary endpoint in seronegative and HPV DNA negative subjects at baseline, 5 in the HPV group and 91 in the HAV group and vaccine efficacy remained high (VE= 94.5% [86.2, 98.4],  $p<0.0001$ , [Table 2](#)). Note that the point estimate of vaccine efficacy in TVC-1 is similarly high compared to the ATP cohort for efficacy,

which indicates that the vaccine efficacy is maintained in a heterogeneous group, including women who received vaccine not administered according to the protocol-specified schedule or who developed infections prior to completion of the vaccination series. These efficacy estimates should be considered as conservative, given that the protocol-specified analysis did not consider whether the HPV type detected in the lesion was likely to be responsible for lesion development.

**Table 2 Summary of vaccine efficacy against the primary endpoint, CIN2+ associated with HPV-16/18, in subjects HPV DNA negative and seronegative at baseline**

	HPV	HAV	VE			
Endpoint Associated with HPV-16/18	n/N	n/N	%	LL	UL	P-value
CIN2+ (ATP)	4/7344	56/7312	92.9	79.9	98.3	<0.0001
CIN2+ (TVC-1)	5/8040	91/8080	94.5	86.2	98.4	<0.0001
CIN2+ (ATP TAA)	1/7344	53/7312	98.1	88.4	100	<0.0001
CIN2+ (TVC-1 TAA)	2/8040	87/8080	97.7	91	99.8	<0.0001
<b>Associated with HPV-16</b>						
CIN2+ (ATP)	2/6303	46/6165	95.7	82.9	99.6	<0.0001
CIN2+ (TVC-1)	3/6921	73/6923	95.9	87	99.3	<0.0001
CIN2+ (ATP TAA)	0/6303	45/6165	100	91	100	<0.0001
CIN2+ (TVC-1 TAA)	1/6921	71/6923	98.6	91.5	100	<0.0001
<b>Associated with HPV-18</b>						
CIN2+ (ATP)	2/6794	15/6746	86.7	39.7	98.7	0.0013
CIN2+ (TVC-1)	2/7455	24/7480	91.6	64.6	99.2	<0.0001
CIN2+ (ATP TAA)	1/6794	13/6746	92.3	45.7	99.9	0.0009
CIN2+ (TVC-1 TAA)	1/7455	22/7480	95.4	70.1	99.9	<0.0001

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots), CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer (ICC), TAA = HPV type assignment algorithm (This analysis is exploratory and is shown in italics).

N = number of subjects included in each group, n = number of subjects reporting at least one event in each group, Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1, VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits, P-value = Two-sided Fisher Exact test

### Results of secondary endpoints (virological and histopathological endpoints associated with HPV-16/18)

The vaccine efficacy against 6-month and 12-month persistent infection (secondary endpoints) and incident infection (exploratory endpoint) with HPV-16/18, HPV-16 and HPV-18 was statistically significant in all analyses in subjects who were HPV DNA negative and seronegative at baseline, with high point estimates and lower limits above zero for all the 96.1% CIs, in the ATP cohort for efficacy (**Error! Reference source not found.** (Synopsis Table 3 in the Clinical Study Report for HPV-008)). The high level of vaccine efficacy against virological endpoints supports the results for histopathological endpoints associated with HPV-16/18 (**Error! Reference source not found.**). Similar levels of vaccine efficacy were seen in TVC-1, where

some of the persistent infections with HPV-16/18 were detected at the Month 6 visit, and therefore were acquired before the subjects had received the third vaccine dose.

**Table 3 Summary of vaccine efficacy against virological and histopathological endpoints associated with HPV-16/18 in subjects HPV DNA negative and seronegative at baseline (ATP cohort for efficacy)**

Endpoint	HPV n/N	HAV n/N	VE %	LL	UL	P-value
<b>Associated with HPV-16/18</b>						
Incident infection	263/7346	1074/7320	76.7	73.2	79.9	<0.0001
Persistent infection (6-month)	32/7177	497/7122	93.8	91	95.9	<0.0001
Persistent infection (12-month)	21/7035	233/6984	91.2	85.9	94.8	<0.0001
Any cytological abnormality (ASC-US+)	51/7340	434/7312	88.5	84.4	91.7	<0.0001
VIN/VaIN1+	2/7344	10/7312	80	0.3	98.1	0.0221
CIN1+	8/7344	96/7312	91.7	82.4	96.7	<0.0001
CIN1+ (TAA)	2/7344	90/7312	97.8	91.4	99.8	<0.0001
CIN3+	2/7345	10/7312	80	0.3	98.1	0.0221
CIN3+ (TAA)	0/7344	8/7312	100	36.4	100	0.0038
<b>Associated with HPV-16</b>						
Incident infection	139/6304	687/6172	80.9	76.8	84.4	<0.0001
Persistent infection (6-month)	23/6163	345/6018	93.7	90.1	96.1	<0.0001
Persistent infection (12-month)	18/6052	175/5903	90.1	83.5	94.4	<0.0001
Any cytological abnormality (ASC-US+)	33/6299	279/6165	88.6	83.3	92.4	<0.0001
VIN/VaIN1+	2/6303	6/6165	67.2	-97	97.2	0.1749
CIN1+	5/6303	70/6165	93	82.2	97.9	<0.0001
CIN1+ (TAA)	1/6303	66/6165	98.5	91	100	<0.0001
CIN3+	2/6303	6/6165	67.2	-97.1	97.2	0.1749
CIN3+ (TAA)	0/6303	6/6165	100	8.8	100	0.0146
<b>Associated with HPV-18</b>						
Incident infection	134/6796	509/6751	74.4	68.7	79.3	<0.0001
Persistent infection (6-month)	9/6642	188/6567	95.3	90.7	98	<0.0001
Persistent infection (12-month)	3/6508	70/6440	95.8	86.6	99.2	<0.0001
Any cytological abnormality (ASC-US+)	20/6790	204/6746	90.3	84.4	94.4	<0.0001
VIN/VaIN1+	0/6794	4/6746	100	-67	100	0.0616
CIN1+	3/6794	31/6746	90.4	67.7	98.3	<0.0001
CIN1+ (TAA)	1/6794	29/6746	96.6	78.1	99.9	<0.0001
CIN3+	0/6794	5/6746	100	-19.3	100	0.0307
CIN3+ (TAA)	0/6794	3/6746	100	-170.5	100	0.1236

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots) HAV = Hepatitis A vaccine (three lots), ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC, CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC, CIN3+ = CIN3, AIS or ICC; TAA = type assignment algorithm;

N = number of subjects included in each group, n = number of subjects reporting at least one event in each group  
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for HPV-16 or HPV-18, VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits, P-value = Two-sided Fisher Exact test.

Results for CIN2+ are shown in [Table 2](#)

***Reviewer's comments:** I checked the VEs and the corresponding 96.1% CIs in the previous two tables, using the StatXact and my own SAS programs, based on the information provided by the applicant including the number of subjects reporting at least one event in each group (n) and the sum of follow-up period expressed in year censored at the first occurrence of event in each group (T(year)). In Table 3, VE was calculated based on the person-year rates (not the total N).*

## **II.3 Study HPV-007**

### **Study Design**

HPV-007 is a phase IIb, blinded, multi-center, long-term follow-up study of the efficacy of candidate HPV-16/18 L1/AS04 vaccine in the prevention of HPV-16 and/or HPV-18 cervical infection in adolescent and young adult women in North America and Brazil vaccinated in primary study HPV-001.

#### **Summary of study HPV-001:**

Eligible subjects were healthy adolescent and young adult women in North America (USA and Canada) and Brazil, between the ages of 15 and 25 years, who had normal cervical cytology and who were HPV-16 and HPV-18 seronegative by ELISA and oncogenic HPV DNA negative by PCR at screening. 1113 subjects were enrolled and randomized (1:1) to receive either the HPV-16/18 L1/AS04 vaccine (20 µg HPV-16 L1 protein, 20 µg HPV-18 L1 protein, 500 µg aluminum hydroxide and 50 µg 3-*O*-desacyl-4'-monophosphoryl lipid A [MPL]) or the placebo control (500 µg aluminum hydroxide), administered intramuscularly according to a 0, 1, 6-month schedule. All subjects were followed for 18 to 27 Months. All efforts were made to keep the study blind for the long-term follow-up.

#### **Summary of study HPV-007:**

- Thirty-six months of long-term follow-up, with seven scheduled visits (i.e., every six months). Study HPV-007 started approximately **three years post vaccination**.
- Blinding was maintained for subjects and investigators and their study staff with regard to the individual subject treatment assignments allocated in study HPV-001.
- Blood samples were collected at Months 0, 12, 24 and 36.
- Cervical liquid-based cytology samples were collected at each visit for HPV PCR testing (at 6-month intervals) and cytological evaluations (at one year intervals, or 6-month intervals if driven by clinical management algorithm) for three years (36 months).
- Cervical swabs were collected for *Chlamydia trachomatis* and *Neisseria gonorrhea* testing on a yearly schedule. This testing was performed for clinical management only (no related study endpoints).

- **Two interim analyses** were conducted: at Month 12 (reported February 2006) and Month 24 (reported December 2006).

## **Objectives**

### **Primary:**

To evaluate the long-term vaccine efficacy in the prevention of incident cervical infection with HPV-16 and/or HPV-18 (by polymerase chain reaction [PCR]) in adolescent and young adult women who received three doses of the study vaccine or placebo in study HPV-001 and who were previously uninfected with HPV-16 or HPV-18.

### **Secondary:**

- To evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (6-month definition) with HPV-16 and/or HPV-18 (by PCR) in adolescent and young adult women who received three doses of the study vaccine/placebo in study HPV-001 and who previously did not have persistent cervical infection (i.e. 6 months) with HPV-16 or HPV-18 in study HPV-001.
- To evaluate the long-term vaccine efficacy in the prevention of persistent cervical infections (6-month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR) in adolescent and young adult women who received three doses of the study vaccine/placebo in study HPV-001 and who previously did not have persistent cervical infection (i.e., 6 months) with that HPV type in study HPV-001.
- To evaluate the long-term vaccine efficacy in the prevention of incident cervical infections with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR) in adolescent and young adult women who received three doses of the study vaccine/placebo in study HPV-001 and who were previously uninfected by that type.
- To evaluate the long-term vaccine efficacy in the prevention of histopathologically-confirmed cervical intraepithelial neoplasia (CIN)1+ or CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).
- To evaluate the long-term vaccine efficacy in the prevention of histopathologically-confirmed CIN1+ or CIN2+ associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) detected within the lesional component of the cervical tissue specimen (by PCR).
- To evaluate the long-term vaccine efficacy in the prevention of abnormal cytology (atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesion [LSIL], high-grade squamous intraepithelial lesion [HSIL], atypical glandular cells [AGC], atypical squamous cells cannot exclude HSIL [ASC-H]) associated with an HPV-16 and/or HPV-18 cervical infection.

- To evaluate the long-term vaccine efficacy in the prevention of abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) (by PCR).

### **Endpoints**

Primary endpoint: Incident cervical infection with HPV-16 and/or HPV-18.

Secondary endpoints:

- Persistent cervical infection (6-month definition) with HPV-16 and/or HPV-18.
- Persistent cervical infection (6-month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Incident cervical infection with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Histopathologically-confirmed CIN1+ or CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).
- Histopathologically-confirmed CIN1+ or CIN2+ associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) detected within the lesional component of the cervical tissue specimen (by PCR).  
CIN1+ is defined as CIN1, CIN2, CIN3, adenocarcinoma in situ (AIS) and invasive cervical cancer. CIN2+ is defined as CIN2, CIN3, AIS and invasive cervical cancer.
- Abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with an HPV-16 and/or HPV-18 cervical infection.
- Abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) cervical infection.

### **Analysis Cohorts**

The According-to-Protocol (ATP) cohort for analysis of efficacy included all subjects for whom differential treatment effect on efficacy was likely (i.e. those meeting all eligibility criteria in studies HPV-001 and HPV-007), complying with the procedures defined in the HPV-001 and HPV-007 protocols, and for whom data concerning efficacy endpoint measures were available.

The following criteria were to be checked at each visit subsequent to the first visit in study HPV-007. If any became applicable during the study, it did not require withdrawal of the subject from the study but subjects were to be eliminated from the ATP analysis for efficacy.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (For corticosteroids, this meant prednisone  $\geq 0.5$  mg/kg/day, or equivalent. Administration of inhaled and/or topical steroids was not considered a criterion that influenced a subject's eligibility for valuation in the ATP cohort).
- Administration of any HPV vaccine other than that used in study HPV-001 during the study period.



In addition, for each type of endpoint (incident infection, persistent infection, abnormal cytology or CIN lesions) subjects could not have encountered the equivalent or higher endpoint associated with the corresponding HPV-type in the study HPV-001.

The Total cohort included all enrolled subjects who came at the first visit in study HPV-007. For the Total analysis of efficacy, this included enrolled subjects for whom data concerning efficacy endpoint measures were available.

In addition, for each type of efficacy endpoint (incident infection, persistent infection, abnormal cytology or CIN lesions) subjects could not have encountered the equivalent or higher endpoint associated with the corresponding HPV-type in the study HPV-001.

### **Statistical methods**

Data evaluations were performed on two defined study cohorts: ATP cohort and Total cohort.

Vaccine efficacy and 95% confidence intervals (CIs) were calculated using Conditional exact method for both ATP and Total cohorts. Incidence rates were compared between groups using Fisher's exact test. The null hypothesis was that the expected incidence rate during the considered period was similar in both groups. In addition, comparison between groups was measured by the time-to-occurrence approach using a log rank test. The magnitude of vaccine effect was estimated in terms of vaccine efficacy (with 95% CI) obtained from a Cox regression.

A pre-specified combined (pooled) analysis of efficacy data of HPV-001 and HPV-007 was performed as well. The same methods as described above were used for the combined (pooled) analysis, except that the analysis was descriptive (p-values were not calculated); for each endpoint, the point estimates of the vaccine efficacy (with 95% CI) were provided.

### **Changes to planned efficacy analysis**

Individual listings are not provided at the final analysis in order to maintain the blind for subjects and investigators from the Brazilian cohort participating in the follow-up study HPV-023.

For virological endpoints, analyses were performed on the ATP cohort for efficacy (primary analysis) and on the Total cohort as defined in the protocol. For cytological and histopathological endpoints, however, the efficacy analysis performed on the Total cohort was considered as primary, due to the limited number of cases obtained during this study. The ATP cohort supplemented the analysis of these endpoints.

In study HPV-001, the follow-up period differed among subjects and in study HPV-007 subjects were enrolled on dates that were independent from the date of their enrollment in study HPV-001 (first vaccine dose administration). As a result, the proposed attack rate method for the efficacy analysis was not adequate. Therefore, the Cochran-Mantel- Haenszel statistic (as originally planned in the protocol) was replaced by the Conditional exact method. The Cox regression method, which models the time-to-occurrence, was presented as confirmatory analysis.

Vaccine efficacy was calculated using incidence rates and using all subjects that had at least one visit in HPV-007 with available efficacy data. Vaccine efficacy was defined as 1 minus the rate ratio.

## **Study Results**

Of the 1113 women initially enrolled in study HPV-001, a total of 776 subjects were enrolled in the long-term follow-up study HPV-007: 393 subjects who received the HPV- 16/18 L1/AS04 vaccine and 383 subjects who received the placebo control (in study HPV-001).

The mean follow-up period from the start of study HPV-001 until the end of study HPV-007 (Month 36) was **5.9** years, i.e., 2164.1 days (standard deviation of 98.31 days), with a maximum duration of **6.4** years, i.e., 2341.0 days.

### **Results of primary and highlighted endpoints**

The primary objective of the study was prevention of incident cervical infection with HPV-16 and/or HPV-18 in women who received three doses of vaccine in study HPV-001 and who were considered as uninfected with HPV-16 or HPV-18 at the time of vaccination.

**Table** (Table 13 in the Clinical Study Report for HPV-007) shows the incidence rates and vaccine efficacy against incident infection with HPV-16 and/or HPV-18 in study HPV-007. The observed vaccine efficacy (VE) against HPV-16 and/or HPV-18 infection was statistically significant (VE = 96.7% [87.4%, 99.6%],  $p < 0.0001$ ). In addition, there was clear evidence of protection against HPV-16 infection alone (VE = 97.5% [85.3%, 99.9%],  $p < 0.0001$ ) and HPV-18 infection alone (VE = 96.3% [77.5%, 99.9%],  $p < 0.0001$ ).

**Table 4 Incidence rates and vaccine efficacy against incident infection with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Cervical samples only, ATP cohort for efficacy)**

Event Type	Group	N	n	T (year)	Person-year Rate			VE			P-value
					n/T (Per 100)	LL	UL	%	LL	UL	
HPV-16/18	Vaccine	303	2	830.25	0.2	0.0	0.9	96.7	87.4	99.6	<0.0001
	Placebo	267	47	644.66	7.3	5.4	9.7				
HPV-16	Vaccine	304	1	833.70	0.1	0.0	0.7	97.5	85.3	99.9	<0.0001
	Placebo	270	33	676.11	4.9	3.4	6.9				
HPV-18	Vaccine	303	1	832.31	0.1	0.0	0.7	96.3	77.5	99.9	<0.0001
	Placebo	281	24	731.50	3.3	2.1	4.9				

Vaccine = HPV-16/18 L1/AS04

Placebo = Aluminum hydroxide

N = number of subjects included in each group

Subjects with an event who did not report the same event in HPV-001

n = number of subjects reporting at least one event in each group

Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001

T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group

n/T = person-year rate in each group

LL, UL = 95% Lower and Upper confidence limits

VE(%) = Vaccine Efficacy (Conditional exact method)

P-value is based on the Fisher exact test

**Table** (Table 31 in the Clinical Study Report for HPV-007) shows the overall incidence rates and vaccine efficacy against any cytological abnormality ( $\geq$  ASC-US, i.e. ASC-US, LSIL, HSIL, AGC or ASC-H) associated with HPV-16 and/or HPV-18 in study HPV-007. The observed vaccine efficacy against cytological abnormalities ( $\geq$  ASC-US) associated with HPV-16 and/or HPV-18 was statistically significant (VE = 100% [87.4%, 100%],  $p < 0.0001$ ). The observed vaccine efficacy against cytological abnormalities associated with HPV-16 or HPV-18 alone was also statistically significant (VE = 100% [82.0%, 100%],  $p < 0.0001$  and VE = 100% [63.2%, 100%],  $p = 0.0003$ , respectively).

**Table 5 Incidence rates and vaccine efficacy against cytological abnormalities (greater than or equal to ASC-US) associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort)**

Event Type	Group	N	n	T (year)	Person-year Rate			VE			P-value
					n/T (Per 100)	LL	UL	%	LL	UL	
HPV-16/18	Vaccine	357	0	976.60	0.0	0.0	0.4	100.0	87.4	100.0	< 0.0001
	Placebo	324	27	837.56	3.2	2.1	4.7				
HPV-16	Vaccine	357	0	976.60	0.0	0.0	0.4	100.0	82.0	100.0	< 0.0001
	Placebo	330	20	865.80	2.3	1.4	3.6				
HPV-18	Vaccine	358	0	978.51	0.0	0.0	0.4	100.0	63.2	100.0	0.0003
	Placebo	337	11	903.61	1.2	0.6	2.2				

Vaccine = HPV-16/18 L1/AS04; Placebo = Aluminum hydroxide

N = number of subjects included in each group

Subjects with an event who did not report the same event in HPV-001

n = number of subjects reporting at least one event in each group

Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001

T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group Follow-up period starts at Month 0 for HPV-001, interval period between end of HPV-001 and beginning of HPV-007 is censored

n/T = person-year rate in each group

LL, UL = 95% Lower and Upper confidence limits

VE(%) = Vaccine Efficacy (Conditional exact method)

P-value is based on the Fisher exact test

**Table 4** (Table 37 in the Clinical Study Report for HPV-007) shows the overall incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 in study HPV-007. The observed vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 was statistically significant (VE = 100% [52.6%, 100%],  $p = 0.0014$ ). The observed vaccine efficacy against CIN1+ associated with HPV-16 or HPV-18 alone was also statistically significant.

**Table 4 Incidence rates and vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort)**

Event Type	Group	N	n	T (year)	Person-year Rate			VE			P-value
					n/T (Per 100)	LL	UL	%	LL	UL	

HPV-16/18	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	52.6	100.0	0.0014
	Placebo	339	9	913.20	1.0	0.5	1.9				
HPV-16	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	34.8	100.0	0.0062
	Placebo	339	7	916.44	0.8	0.3	1.6				
HPV-18	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	-132.3	100.0	0.1177
	Placebo	345	3	936.12	0.3	0.1	0.9				

Vaccine = HPV-16/18 L1/AS04; Placebo = Aluminum hydroxide

N = number of subjects included in each group

Subjects with an event who did not report the same event in HPV-001

n = number of subjects reporting at least one event in each group

Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001

T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group Follow-up period starts at Month 0 for HPV-001, interval period between end of HPV-001 and beginning of HPV-007 is censored

n/T = person-year rate in each group

LL, UL = 95% Lower and Upper confidence limits

VE(%) = Vaccine Efficacy (Conditional exact method)

P-value is based on the Fisher exact test

**Table 5** (Table 40 in the Clinical Study Report for HPV-007) shows the overall incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 in study HPV-007. The observed vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 was statistically significant (VE = 100% [19.7%, 100%], p = 0.0133).

**Table 5 Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) using Conditional exact method (Total cohort)**

Event Type	Group	N	n	T (year)	Person-year Rate			VE			P-value
					n/T (Per 100)	LL	UL	%	LL	UL	
HPV-16/18	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	19.7	100.0	0.0133
	Placebo	342	6	922.22	0.7	0.2	1.4				
HPV-16	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	-129.7	100.0	0.1161
	Placebo	342	3	925.75	0.3	0.8	0.9				
HPV-18	Vaccine	358	0	975.13	0.0	0.0	0.4	100.0	-132.3	100.0	0.1177
	Placebo	345	3	936.12	0.3	0.1	0.9				

Vaccine = HPV-16/18 L1/AS04; Placebo = Aluminum hydroxide

N = number of subjects included in each group

Subjects with an event who did not report the same event in HPV-001

n = number of subjects reporting at least one event in each group

Subjects with an event are DNA negative for the corresponding HPV type at Month 0 in HPV-001

T(year) = sum of follow-up period expressed in year censored at the first occurrence of event in each group Follow-up period starts at Month 0 for HPV-001, interval period between end of HPV-001 and beginning of HPV-007 is censored

n/T = person-year rate in each group

LL, UL = 95% Lower and Upper confidence limits

VE(%) = Vaccine Efficacy (Conditional exact method)

P-value is based on the Fisher exact test

**Reviewer's comments:** I checked the person-year rates, VE, and the corresponding 95% CIs in the previous two tables using the StatExact and SAS programs based on the information provided by the applicant, including the number of subjects reporting at least one event in each

group (n) and the sum of follow-up periods expressed in years, censored at the first occurrence of event in each group (T(year)).

As indicated by the applicant, the Fisher's exact test was used for the comparisons between the two groups.

## II.4 Efficacy Conclusions

In the pivotal study HPV-008, the primary endpoint of the study, prevention of CIN2+ lesions associated with HPV-16 and/or HPV-18 (HPV-16/18), was met with a high level of vaccine efficacy (92.9% [79.9, 98.3],  $p < 0.0001$ ) in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6, with 4 cases in the HPV group and 56 in the HAV group in the ATP cohort for efficacy. Statistically significant vaccine efficacy was also observed for HPV-16 or HPV-18, with high point estimates and the lower limits of the 96.1% CI well above 30% for each type. All other histopathological (CIN3+, CIN1+, ASC-US+, and VIN/VaIN1+) and virological (incident, 6-month, and 12-month persistent infection) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6.

At the final analysis, the average follow up time for the primary endpoint evaluation was approximately 2 years longer than at interim, with a mean follow-up of 2.9 years in the ATP cohort for efficacy and 3.3 years in TVC-1.

In supportive Study HPV-007, statistically significant long-term vaccine efficacy was observed against:

- Incident infection with HPV-16 and/or HPV-18 (**primary objective**): VE = 96.7% [87.4%, 99.6%],  $p < 0.0001$ , ATP cohort
- Cytological abnormalities  $\geq$  ASC-US associated with HPV-16 and/or HPV-18: VE = 100% [87.4%, 100%],  $p < 0.0001$ , Total cohort
- CIN1+ associated with HPV-16 and/or HPV-18: VE = 100% [52.6%, 100%],  $p = 0.0014$ , Total cohort
- CIN2+ associated with HPV-16 and/or HPV-18: VE = 100% [19.7%, 100%],  $p = 0.0133$ , Total cohort

**Reviewer's comments:** 1) The primary endpoint of study HPV-008, prevention of CIN2+ lesions associated with HPV-16 and/or HPV-18 (HPV-16/18), was met; 2) All other histopathological (CIN3+, CIN1+, ASC-US+, and VIN/VaIN1+) were statistically significant in the ATP cohort for efficacy; 3) The virological (incident, 6-month and 12-month persistent infection) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy; however, the clinical meaningfulness of these findings needs to be assessed by the clinical reviewer, Dr. Nancy Miller; 4) As to the findings that the candidate vaccine reduced persistent infection and precancerous lesions or AIS caused by oncogenic HPV types other than HPV-16 and HPV-18, HPV-31 may be the only one that reached statistical significance if an

*adequate Type I error adjustment had been performed. The clinical meaningfulness of these findings is subject to the clinical reviewer's judgment.*

### **III. STATISTICAL REVIEW OF SAFETY**

#### **III.1 Introduction**

This section discusses the safety profile for the candidate vaccine.

#### **III.2 Study HPV-008**

##### Safety objective

To evaluate the safety of the candidate vaccine in adolescent and young adult women, overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and HPV-16/18 antibody status (by ELISA) throughout the entire study period.

##### Safety endpoints

- Occurrence, intensity, relationship to vaccination and resulting school or work absenteeism (as applicable) of any solicited local or solicited general symptoms within 7 days (days 0-6) after each vaccination dose, overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in a subset of subjects from selected study sites (safety diary card subset).
- Occurrence, intensity, relationship to vaccination and resulting school or work absenteeism (as applicable) of any unsolicited symptoms within 30 days (days 0-29) after any vaccination dose, overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in a subset of subjects from selected study sites (safety diary card subset).
- Occurrence of SAEs throughout the entire study period (Month 0 to 48), overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in all subjects.
- Occurrence of New Onset Chronic Diseases (NOCD, e.g., autoimmune disorders, type I diabetes) throughout the entire study period (Month 0 to 48), overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in all subjects.
- Occurrence of medically significant conditions throughout the entire study period (Month 0 to 48), overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA) in all subjects. Medically significant conditions are defined as: adverse events (AEs) prompting emergency room or physician visits that are not (1) related to common diseases or (2) 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, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

- Outcome of all pregnancies throughout the entire study period (Month 0 to 48), overall and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA).

Note: The first two safety endpoints (symptoms within 7 days and 30 days of vaccination) were exclusively assessed at the interim analysis. These results were not repeated at the final analysis, but are presented in this final clinical study report for completeness.

### Analysis of safety

As the final analysis was event-driven, safety endpoints (i.e., SAEs, pregnancy outcomes and AEs related to NOCDs and medically significant conditions) were assessed up to the data lock point (DLP). Note that the analysis of solicited symptoms (days 0-6) and unsolicited symptoms/medications (days 0-29) was performed exclusively at the interim analysis. As no additional doses of vaccine/control were administered since the interim analysis, the reactogenicity analysis was not repeated, but the interim data are presented in this final clinical study report for completeness.

The primary analysis of solicited symptoms was based on the Interim Total Vaccinated cohort for solicited symptoms (safety diary card subset). The primary analysis of safety was based on the Total Vaccinated cohort and included the safety diary card subset (Interim cohort) for solicited (days 0-6) and unsolicited (days 0-29) symptoms after vaccination, and all subjects (Final cohort) for SAEs, NOCDs, medically significant conditions and pregnancies during the entire study period.

A complementary analysis of the solicited symptoms and unsolicited symptoms/medications reported within 30 days after each dose was performed based on the Interim ATP cohort for safety and a complementary analysis of the SAEs, NOCDs, medically significant conditions and pregnancies reported during the entire follow-up period was performed based on the Final ATP cohort for safety to supplement the primary analysis.

All safety and reactogenicity analyses were presented by vaccine group. Additionally, analyses of safety and reactogenicity were done on seronegative and DNA negative subjects for both HPV-16 and HPV-18 at baseline, on seropositive and/or DNA positive subjects for HPV-16 and/or HPV-18 at baseline and on DNA positive subjects for HPV-16 and/or HPV-18 at baseline. The percentage of subjects reporting each individual solicited local and general symptom during the solicited follow-up period was tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general symptom was tabulated, over the whole vaccination course, with exact 95% CI. The analyses of solicited local and general symptoms and unsolicited symptoms were also done by ethnicity.

The proportion of subjects with at least one report of an unsolicited symptom classified by the Medical Dictionary for Regulatory Activities (MedDRA), whenever available, and reported up to 30 days after vaccination was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited symptoms, and for unsolicited symptoms with a possible relationship to vaccination.

The proportion of subjects with at least one report of an NOCD, medically significant condition or SAE classified by MedDRA, whenever available, and reported during the entire study period was tabulated with exact 95% CI. Within the AEs considered as NOCD (GSK assessment), a GSK physician determined whether the AE was an autoimmune disease. The proportion of subjects with at least one report of a New Onset of Autoimmune Disease (NOAD) classified by MedDRA and reported during the entire study period was tabulated with exact 95% CI.

Pregnancies were analyzed during the entire follow-up period and around the time of vaccination and their outcomes were described in detail.

### Study Cohorts for Safety Analyses

Note that part of the safety analyses presented in this final clinical study report was exclusively performed at the interim analysis, but were included for completeness. As a result, the safety analyses presented in this report are based on different cohorts depending on the endpoint analyzed:

- The analysis of solicited symptoms (days 0-6), unsolicited symptoms (days 0-29) and concomitant medication and vaccination (days 0-29) is based on the ATP cohort and Total Vaccinated cohort for safety defined at the interim analysis, referred as “Interim ATP cohort for safety” and “Interim Total Vaccinated cohort for safety” throughout this report.
- The analysis of SAEs, pregnancies, pregnancy outcomes and AEs related to NOCDs and medically significant conditions is based on the ATP cohort and Total Vaccinated cohort for safety defined at the current final analysis, as the follow-up time for these endpoints was much longer. These cohorts are referred to as “Final ATP cohort for safety” and “Final Total Vaccinated cohort for safety” throughout this report.
- Total Vaccinated cohort for safety
  - The Total Vaccinated cohort for safety included all vaccinated subjects for whom data were available for analysis of the safety endpoints. Thus, the Total Vaccinated cohort analysis included all subjects with at least one vaccine administration documented. The Total Vaccinated cohort for the analysis of solicited symptoms included the subset of subjects from selected study sites who completed and returned a safety diary card.
  - The Total Vaccinated cohort for the analysis of unsolicited symptoms included the safety diary card subset for solicited (days 0-6) and unsolicited (days 0-29) symptoms after vaccination, and all subjects for SAEs, NOCD, and medically significant conditions



during the entire study period. The safety analyses were also stratified according to baseline HPV DNA and/or seropositivity status using the following cohorts:

**Vaccinated HPV-16 and HPV-18 seronegative and DNA negative cohort:** The vaccinated seronegative and DNA negative cohort included subjects that belonged to the Total Vaccinated cohort and who were seronegative and DNA negative at baseline (Month 0) for both HPV-16 and HPV-18. This cohort was only used for analysis of safety.

**Vaccinated HPV-16 or HPV-18 seropositive and/or DNA positive cohort:** The vaccinated seropositive and/or DNA positive cohort included subjects that belonged to the Total Vaccinated cohort and who were seropositive and/or DNA positive at baseline (Month 0) for either HPV-16 or HPV-18. This cohort was only used for analysis of safety.

**Vaccinated HPV-16 or HPV-18 DNA positive cohort:** The vaccinated DNA positive cohort included subjects that belonged to the Total Vaccinated cohort and who were DNA positive at baseline (Month 0) for either HPV-16 or HPV-18. This cohort was only used for analysis of safety.

- ATP cohort for analysis of safety

The ATP cohort for safety was based on the Total Vaccinated cohort and included all subjects:

- who had received three doses of study vaccine/control according to their random assignment
- with sufficient data to perform an analysis of safety (at least one dose with safety follow-up)
- for whom administration site of study vaccine/control was known
- who had not received a vaccine not specified or forbidden in the protocol
- for whom the randomization code had not been broken.

### Statistical Methods

All safety and reactogenicity analyses were presented by vaccine group. Additionally, analyses of solicited local and general symptoms and unsolicited symptoms were done on seronegative and DNA negative subjects for both HPV-16 and/or HPV-18 at baseline, on seropositive and/or DNA positive subjects for HPV-16 and/or HPV-18 at baseline, and on DNA positive subjects for HPV-16 and/or HPV-18 at baseline. The analyses of solicited local and general symptoms and unsolicited symptoms were also done by ethnicity at the interim analysis and are included in the final clinical study report for completeness.

No formal comparisons were made between groups.

The safety analyses performed exclusively at the interim analysis, but included in this final clinical study report for completeness, included:

- solicited signs and symptoms (days 0-6) reported,
- unsolicited signs and symptoms (days 0-29) reported,
- concomitant medication and vaccination (days 0-29) reported.

The safety analyses performed at the interim and final analyses included:

- serious adverse events, pregnancies, pregnancy outcomes and adverse events related to NOCD and medically significant conditions reported.

## **Safety Results**

### **Overall incidence of adverse events**

During the 30-day post-vaccination period, the percentage of doses followed by any symptom (solicited and unsolicited) was higher in the HPV group than in the HAV group: 85.4% versus 74.6%, respectively. This difference was observed for local symptoms (81.3% versus 61.3%, overall per dose) and to a lesser extent for general symptoms (65.8% versus 59.9%, overall per dose). There was no apparent increase in the incidence of symptoms with subsequent dose(s). The percentage of doses followed by any grade 3 symptom (solicited and unsolicited) during the 30-day post-vaccination period was also higher in the HPV group than in the HAV group: 13.1% and 7%, respectively. This difference was observed for grade 3 local symptoms (8.3% versus 2%, overall per dose) and to a lesser extent for grade 3 general symptoms (7.3% versus 5.5%, overall per dose). In both groups, the majority of the grade 3 symptoms were transient and resolved within several days of vaccination

Additionally, the incidence of solicited and unsolicited symptoms assessed as possibly related to vaccination according to the investigator and the incidence of grade 3 symptoms (solicited and unsolicited) assessed as possibly related to vaccination according to the investigator was higher in the HPV group (83.1% and 9.9%, respectively, overall per dose) compared to the HAV group (67.9% and 3.9%, overall per dose).

The incidence of solicited and unsolicited symptoms observed for subjects who were seropositive and/or DNA positive for either HPV-16 or HPV-18 at baseline, seronegative and DNA negative for HPV-16 and HPV-18 at baseline, or DNA positive for either HPV-16 or HPV-18 at baseline was comparable to the incidence observed for the Total Vaccinated cohort.

### **Solicited local adverse events**

The percentage of doses followed by solicited local symptoms during the 7-day post-vaccination period was higher in the HPV group compared to the HAV group. The incidence of grade 3 solicited local symptoms during the 7-day postvaccination period was also higher in the HPV group compared to the HAV group.

Pain was the most frequently reported solicited local symptom in both groups. Overall, 90.5% and 78.0% of subjects reported pain at the injection site in the HPV and HAV groups, respectively, following 80.2% and 58.9% of doses. Grade 3 pain was reported after 7.3% of doses in the HPV group compared to 1.8% of doses in the HAV group. The incidence of pain at the injection site did not increase with subsequent doses in either group.

Overall, redness at the injection site was reported by 43.8% and 27.6% of subjects after 28.1% and 16.0% of doses in the HPV and HAV groups, respectively. Swelling at the injection site was reported by 42.0% and 19.8% of subjects after 25.4% and 10.1% of doses, respectively. Grade 3 redness and swelling (>50 mm) were infrequently reported after at most 1% of doses administered in the HPV group and at most 0.2% of doses in the HAV group. In the HPV group, the incidence of redness and swelling slightly increased from dose to dose (i.e., from 22.0% and 25.4% at Dose 1 to 30.8% and 32.4% at Dose 3, for redness and swelling, respectively).

However, despite the higher incidence of solicited local symptoms in the HPV group, no impact on compliance for completion of the three-dose vaccination schedule was observed (91.6% in the HPV group and 91.9% in the HAV group).

#### Solicited general adverse events

Overall, the incidence of solicited general symptoms within 7 days after vaccination was slightly higher in the HPV group compared to the HAV group. The incidence of solicited general symptoms assessed as grade 3, as possibly related to vaccination according to the investigator and as grade 3 and possibly related to vaccination according to the investigator was also higher in the HPV group compared to the HAV group. The CIs calculated for the percentage of doses followed by solicited symptoms were extremely narrow because of the large sample size. Some of these difference may be statistically significant. However, whether these differences are medically meaningful will be determined by the clinical reviewer, Dr. Nancy Miller.

The most frequently reported solicited general symptoms in both groups were fatigue, myalgia, and headache:

- Fatigue was reported by 57.6% and 53.6% ( $p=0.001873$ ) of subjects following 38.8% and 35.3% ( $p < 0.0001$ ) of doses in the HPV and HAV groups, respectively. Grade 3 fatigue was reported following 1.6% and 1.3% ( $p=0.051$ ) of doses, respectively.
- Myalgia was reported by 52.2% and 44.9% ( $p<0.0001$ ) of subjects following 34.3% and 26.5% ( $p<0.0001$ ) of doses in the HPV and HAV groups, respectively. Grade 3 myalgia was reported following 1.8% and 0.6% ( $p<0.0001$ ) of doses, respectively.
- Headache was reported by 54.1% and 51.3% ( $p=0.0245$ ) of subjects following 32.9% and 30.8% ( $p=0.00273$ ) of doses in the HPV and HAV groups, respectively. Grade 3 headache was reported following 1.7% and 1.4% ( $p=0.0645$ ) of doses, respectively.

***Reviewer's comments:*** In response to Dr. Horne's request for some statistical analyses of the safety outcomes, I obtained all the 2-sided  $p$ -values by using the Barnard's test for comparison

*of two binomial proportions. These p-values should be interpreted with caution as they are results of post hoc analyses without any multiplicity adjustment.*

### Unsolicited adverse events

During the 30-day post-vaccination period, unsolicited symptoms were reported by a similar number of subjects and after a similar number of doses in both groups. Overall, 42.5% and 43.6% of subjects reported at least one unsolicited symptom after 21.6% and 22.4% of doses in the HPV and HAV groups, respectively. Also, a similar percentage of subjects in both groups reported unsolicited symptoms assessed as grade 3, as possibly related to vaccination by the investigator, or as grade 3 and possibly related to vaccination by the investigator after a similar percentage of doses. The number of unsolicited symptoms assessed as possibly related to vaccination according to the investigator was higher in the HPV group compared to the HAV group. This difference can partially be attributed to the higher number of injection site nodule and pruritus reported in the HPV group.

The most common unsolicited symptoms ( $\geq 1\%$  of doses in both groups) were headache, influenza, gynecological Chlamydia infection, nasopharyngitis, pharyngolaryngeal pain and dizziness. All these events were reported by a similar number of subjects after a similar percentage of doses in both groups.

### Serious adverse events

At the time of the final analysis, 1724 SAEs were reported in 1400 subjects, of whom 701 subjects were in the HPV group and 699 subjects were in the HAV group (Table 6). The number of doses followed by one or more SAEs and the number of events experienced were also similar between both groups.

**Table 6 Global summary of Serious Adverse Events reported (Total Vaccinated cohort)**

	Group		Total
	HPV	HAV	
	N=1804	N=1802	
Number of subjects with at least one SAE reported	701	699	1400
Number of doses followed by at least one SAE	719	720	1439
Number of SAEs classified by MedDRA Preferred Term*	862	825	1687
Number of SAEs reported	882	842	1724

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HAV = Hepatitis A vaccine (three lots)

N: Number of subjects in each group

\*Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

### Fatal events

At the time of the final analysis, 20 fatal events were reported for 17 subjects (nine in the HPV group and eight in the HAV group). Road traffic accidents were the most common causes of death. None of the fatal events were assessed as possibly related to vaccination by the investigator.

## Pregnancies

During the entire follow-up period, 3606 pregnancies were reported (1804 in the HPV group and 1802 in the HAV group) for 3091 subjects (1538 in the HPV group and 1553 in the HAV group). The outcomes of these pregnancies are detailed in [Table 7](#) (Table 123 in HPV-008 Final Report, February 2009).

During the entire follow-up period, no major differences in the rates of any specific pregnancy outcome were observed between the HPV and HAV groups. The overall rate of spontaneous abortion was 8.9% (see [Table 7](#)). The number of spontaneous abortions was 164 in the HPV group and 156 in the HAV group, corresponding to a proportion of pregnancies ending in abortion of 9.1% and 8.7%, respectively (difference of (HPV-HAV) = 0.4%, 95% CI = (-1.1%, 2.0%)).

**Table 7 Number of subjects with pregnancies (overall) and their outcome (Total Vaccinated cohort)**

		HPV		HAV		Total	
		N = 1804		N = 1802		N = 3606	
Characteristics	Categories	n	%	n	%	n	%
Outcome	Normal infant	1124	62.3	1136	63.0	2260	62.7
	Premature birth (healthy)	51	2.8	45	2.5	96	2.7
	Abnormal infant	21	1.2	19	1.1	40	1.1
	Elective termination	185	10.3	194	10.8	379	10.5
	Therapeutic abortion	2	0.1	1*	0.1	3	0.1
	Ectopic pregnancy	15	0.8	6	0.3	21	0.6
	Spontaneous abortion	164	9.1	156	8.7	320	8.9
	Still birth	14	0.8	9	0.5	23	0.6
	Lost to follow up	20	1.1	23	1.3	43	1.2
	Not applicable	4	0.2	1	0.1	5	0.1
	Pregnancy ongoing	204	11.3	212	11.8	416	11.5

HAV = Hepatitis A vaccine (three lots)

N = number of pregnancies

n = number of pregnancies in a given category

% = (n / N) x 100

Abnormal infant includes congenital anomalies and/or other medically significant outcomes in offspring.

Therapeutic abortion: not due to congenital abnormalities

Spontaneous abortion includes missed abortion.

Twin pregnancies are counted as one pregnancy and the worst pregnancy outcomes have been considered.

Not applicable: e.g. mole, trophoblastic tumor

One case of therapeutic abortion, which was reported in the interim analysis, has been re-classified as abnormal infant in the final analysis.

**Table 8 Number of subjects with pregnancies around vaccinations and their outcome (Total Vaccinated cohort)**

		HPV		HAV		Total	
		N = 190		N = 179		N = 369	
Characteristics	Categories	n	%	n	%	n	%

Outcome	Normal infant	116	61.1	127	70.9	243	65.9
	Premature birth (healthy)	8	4.2	5	2.8	13	3.5
	Abnormal infant	1	0.5	4*	2.2	5	1.4
	Elective termination	36	18.9	27	15.1	63	17.1
	Therapeutic abortion	0	0	1	0.6	1	0.3
	Ectopic pregnancy	2	1.1	1	0.6	3	0.8
	Spontaneous abortion	22**	11.6	9*	5	31	8.4
	Still birth	1	0.5	0	0	1	0.3
	Lost to follow up	4	2.1	5	2.8	9	2.4
	Not applicable	0	0	0	0	0	0
	Pregnancy ongoing	0	0	0	0	0	0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)

HAV = Hepatitis A vaccine (three lots)

N = number of pregnancies around vaccination

n = number of pregnancies in a given category

% = (n / N) x 100

Pregnancies around vaccinations: Pregnancy in subjects for which last menstrual period occurred between 30 days before and 45 days after vaccination (subjects with missing date for last menstrual period are not included)

Abnormal infant includes congenital anomalies and/or other medically significant outcomes in offspring.

Therapeutic abortion: not due to congenital abnormalities

Spontaneous abortion includes missed abortion

Twin pregnancies are counted as one pregnancy and the worst pregnancy outcomes have been considered.

Not applicable: e.g. mole, trophoblastic tumor

\* For one case of abnormal infant and spontaneous abortion included in the interim analysis, the date of LMP was changed to “unknown” based on follow-up information received after the interim analysis. These cases are therefore excluded from the final analysis of pregnancy outcomes around vaccination.

\*\* One case of spontaneous abortion was reported for a pregnancy that was ongoing at the time of the interim analysis.

A higher rate of elective terminations in the HPV group versus the HAV group was observed when restricting the analysis to pregnancies around vaccinations (18.9% versus 15.1%, see [Table 8](#), Table 125 in HPV-008 Final Report, February 2009) (difference of (HPV-HAV) = 3.9%, 95% CI = (-2.5%, 10.2%)). When considering the distribution of specific outcomes by treatment group from a descriptive perspective, a higher rate of abnormal infant pregnancy-related outcomes was observed in the HAV group compared to the HPV group (4 [2.2%] versus 1 [0.5%] cases, see [Table 8](#)) (difference of (HPV-HAV) = -1.7%, 95% CI = (-4.4%, 0.4%)), whereas a higher rate of spontaneous abortions was observed in the HPV group compared to the HAV group (22 [11.6%] versus 9 [5.0%] cases) (difference of (HPV-HAV) = 6.6%, 95% CI = (1.9%, 11.5%)).

**Reviewer’s comments:** *In response to Dr. Horne’s request for statistical analyses of the safety outcomes, I obtained all the differences and the corresponding confidence intervals. These statistics should be interpreted with caution as they are results of post hoc analyses without any multiplicity adjustment.*

### III.3 Study HPV-007

Evaluation of the safety of the candidate vaccine in study HPV-001 during the long-term follow-up period of study HPV-007 was listed as one of the “other objectives” (i.e., other than primary and secondary objectives).

The following adverse events (AEs) that occurred between the last visit of study HPV-001 and entry into study HPV-007 and throughout the entire HPV-007 study period were to be recorded:

- Serious adverse events (SAEs).
- Medically significant AEs, i.e., conditions prompting either emergency room visits or physician visits that were not related to common diseases. Common diseases included: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, vaginitis, vulvitis, menstrual cycle abnormalities, and injury.
- New onset chronic diseases (NOCs), e.g. diabetes mellitus, autoimmune diseases.

The investigator (or designee) was to make an assessment of intensity for all AEs, including SAEs, reported during the study. The assessment was to be based on the investigator’s (or designee’s) clinical judgment. The intensity of each AE and SAE was to be assigned to one of the following categories:

- 1 (mild) = An AE that was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- 2 (moderate) = An AE that was sufficiently discomforting to interfere with normal everyday activities.
- 3 (severe) = An AE that prevented normal, everyday activities. (In adults/ adolescents, such an AE would, for example, prevent attendance at work/ school and would necessitate the administration of corrective therapy).

An SAE was any medical occurrence that:

- a. resulted in death,
- b. was life-threatening,
- c. required hospitalization or prolongation of existing hospitalization,
- d. resulted in disability/incapacity,
- e. was a congenital anomaly/birth defect in the offspring of a study subject.
- f. Medical or scientific judgment was to be exercised in deciding whether reporting was appropriate in other situations, such as important medical events that might not have been immediately life-threatening or resulted in death or hospitalization but might have jeopardized the subject or might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

### Pregnancies

The investigator (or designee) was to report pregnancy information on any subject who became pregnant between the last visit of HPV-001 and before the start of HPV-007, and during the entire study period on the Pregnancy Report Form and to submit it to GSK Biologicals within 24 hours of learning of a subject’s pregnancy. The subject was to be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether it was full-term or terminated

prematurely, information on the status of the mother and child was to be forwarded to GSK Biologicals. Follow-up occurred in most of the cases within six to eight weeks following the delivery date.

While pregnancy itself was not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons was to be recorded as an AE or SAE. A **spontaneous abortion** was always to be considered as SAE.

### Study Cohorts for Safety Analyses

Analysis of safety was performed on the ATP cohort for safety (primary analysis) and the Total cohort with data collected from the end of study HPV-001 throughout the entire HPV-007 study period.

### Statistical Methods for Analysis of Safety

Occurrence of AEs, NOCDs, and SAEs recorded between the last visit of study HPV-001 and entry into study HPV-007 and throughout the entire study period of HPV-007 was tabulated.

The proportion of subjects with at least one report of an AE classified by MedDRA (Medical Dictionary for Regulatory Activities), whenever available, was tabulated with exact 95% CI.

Investigators were asked to identify in the eCRF AEs that they considered as NOCD. An analysis of these events was performed (investigator assessment). The proportion of subjects with at least one report of NOCD classified by MedDRA, whenever available, is tabulated with exact 95% CI. A separate table was produced for NOCD based on the Investigator assessment and GSK assessment, respectively.

An additional analysis of New Onset Autoimmune Diseases (NOADs, a subset of NOCDs) was performed.

### Safety Results

The safety profile in the vaccine group was similar to that of the placebo group with overall fewer events reported in the vaccine group for most analyses.

- (1) Adverse Events (ATP cohort for safety: N=373 in the vaccine group, N=369 in the placebo group): The incidence of all AEs recorded by the investigator was slightly lower in the vaccine group compared to the placebo group: 106 subjects (28.4%) reported a total of 141 events in the vaccine group, while 123 subjects (33.3%) reported a total of 199 events in the placebo group.
- (2) New Onset Chronic Diseases (NOCDs; ATP cohort for safety): The number of subjects with reports of an NOCD (assessed by GSK) was similarly low in the vaccine and placebo groups (5 [1.3%] and 6 [1.6%] subjects, respectively). Only one NOCD (pneumonitis) was considered as serious.



The number of subjects with reports of an NOCD based on investigator's assessment was similar in the vaccine group (18 subjects, 4.8%) and the placebo group (21 subjects, 5.7%).

- (3) New Onset Autoimmune Diseases (NOADs; ATP cohort for safety): NOCDs classified as NOADs were reported for two subjects in the vaccine group (0.5%) and four subjects (1.1%) in the placebo group and included hypothyroidism, autoimmune thyroiditis and ulcerative colitis.
- (4) Serious Adverse Events (Total cohort: N=393 in the vaccine group, N=383 in the placebo group): The incidence of SAEs was slightly lower in the vaccine group compared to the placebo group: 31 subjects (7.9%) reported a total of 36 SAEs in the vaccine group, while 39 subjects (10.2%) reported a total of 46 SAEs in the placebo group. None of the SAEs were considered as related to vaccination by the investigator. No fatal events were reported.
- (5) Pregnancies (Total cohort): A total of 261 pregnancies (130 in the vaccine group and 131 in the placebo group) were reported by 217 subjects. The number of pregnancies resulting in abnormal outcomes was lower in the vaccine group compared to the placebo group (19 vs. 29 cases of spontaneous abortion, abnormal infant, elective termination, missed abortion or still birth).

### III.4 Safety Conclusions

In Study HPV-008, the reactogenicity and safety profile of the HPV group was similar to that of the HAV group with the exception of solicited symptoms, which were more frequently reported in the HPV group.

The observed rate of spontaneous abortions following HPV vaccine administration for pregnancies around vaccination was higher in the HPV group than the HAV group (11.6% = 22/190 versus 5.0% = 9/179, difference of (HPV-HAV) = 6.6%, 95% CI = (1.9%, 11.5%)).

**Reviewer's comments:** *Please note that the above post-hoc comparison was done by me in response to Dr. Horne's request for statistical analyses of some of the major safety outcomes. Although the applicant states "Evaluation of all pregnancy outcomes did not show any clinically meaningful differences between the groups," the clinical relevance of this finding should be determined by the clinical reviewer, Dr. Nancy Miller.*

The applicant stated that the HPV-007 safety analysis did not show any clinically relevant differences between the vaccine and placebo groups and therefore indicate that the HPV-16/18 L1/AS04 vaccine has an acceptable long-term safety profile in this population.

## **IV. STATISTICAL REVIEW OF IMMUNOGENICITY**

### **IV.1 Introduction**

Both HPV-008 and HPV007 studies evaluated immune response of the candidate vaccine.

### **IV.2 Study HPV-008**

Immunogenicity subset

Immunogenicity subset included a subset of subjects from selected study sites ( $N \geq 2000$ , at least 500 per region).

All subjects from this subset had additional blood samples taken at Months 6, 12, 36 and 48 for HPV-16/18 serology testing by ELISA and possibly by HPV pseudovirion based neutralization assays (PBNA) and/or monoclonal antibody inhibition enzyme immunoassay.

#### Immunogenicity objectives

- To evaluate vaccine immunogenicity in a subset of subjects from selected study sites (immunogenicity subset), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus.
- To evaluate immune correlates of protection against persistent infections (6- and 12-month definitions) with HPV-16 or Immunogenicity objectives 18 post Dose 3 and CIN2+ associated with HPV-16 or 18 cervical infection (by PCR) post Dose 3 using Month 7 and Month 24 immunogenicity evaluations.

#### Statistical Methods for Analysis of Immunogenicity

The primary analysis was based on the ATP cohort for analysis of immunogenicity. A complementary analysis based on the Total Vaccinated cohort for immunogenicity was performed to supplement the ATP analysis. Anti-HPV-16 and anti-HPV-18 ELISA titers and seroconversion were assessed at baseline in subjects who were seropositive for HPV-16 and HPV-18 at Month 0 and HPV DNA negative for the antigen considered to determine antibody levels following clearance of natural infection.

For each treatment group, at each time point that a blood sample result was available:

- seropositivity rates for HPV-16 and HPV-18 (with exact 95% CI) were calculated by group,
- geometric mean titer (GMT) with 95% CI was tabulated for antibodies for each antigen.

#### Immunogenicity Results

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and on the Total Vaccinated cohort. Analysis of anti-HPV-16 and anti-HPV-18 neutralizing antibodies by PBNA was performed on a subset of subjects who were DNA negative

for HPV-16, 18, 31, 33 and 45 and seronegative for HPV-16 and HPV-18 at Month 0. Analysis of antibody kinetics was performed on subjects in the ATP cohort for immunogenicity who had an ELISA/PBNA result available at all timepoints.

ATP cohort for immunogenicity consisted of 1933 subjects (HPV group: N=1035, HAV group: N=898)

Anti-HPV-16 (Table 9, Table 132 in HPV-008 Final Report, February 2009) and anti-HPV-18 (Table 10, Table 133 in HPV-008 Final Report, February 2009) ELISA:

- High seropositivity rates ( $\geq 99.4\%$ ) were observed for anti-HPV-16 and anti-HPV-18 antibodies up to Month 36, i.e. up to 30 months after completion of the full vaccination course in the HPV group. After a peak response at Month 7, GMTs for anti-HPV-16 and anti-HPV-18 antibodies gradually declined until approximately Month 24 and then reached a plateau level.
- GMTs were well above levels elicited after naturally acquired infection at each timepoint post-vaccination (44.1-fold higher for HPV-16 and 24.5-fold higher for HPV-18 at Month 36).

Overall, the immune responses for subjects who were seronegative for HPV-16 or HPV-18 at baseline and subjects who were seropositive for HPV-16 or HPV-18 at baseline were comparable. Analysis of subjects vaccinated according to varied schedules showed similar immune responses for subjects vaccinated according to a flexible Dose 2 schedule (0, 2, 6-month versus 0, 1, 6-month schedule) and subjects vaccinated according to a flexible Dose 3 schedule (three doses administered within a period of 5, 6, 7, 8, or 9 or more months).

**Table 9 Seropositivity rates and GMTs for anti-HPV-16 antibody titers (ATP cohort for immunogenicity)**

			$\geq 8$ EL.U/ml					GMT				
			N	n	%	95% CI		value	95% CI		Min	Max
Group	Pre-vacc status	Timing				LL	UL		LL	UL		
HPV	S-	PRE	868	0	0	0	0.4	4	4	4	<8.0	<8.0
		PII(M6)	861	860	99.9	99.4	100	627.9	589	669.5	<8.0	13291
		PIII(M7)	861	857	99.5	98.8	99.9	9206.4	8607.2	9847.2	<8.0	187703
		PIII(M12)	835	833	99.8	99.1	100	3282.6	3065.3	3515.3	<8.0	87534
		PIII(M24)	793	792	99.9	99.3	100	1590.4	1490	1697.6	<8.0	36310
		PIII(M36)	780	780	100	99.5	100	1264.6	1184.1	1350.5	25	23557
	S+	PRE	161	161	100	97.7	100	28.6	24.4	33.6	8	502
		PII(M6)	159	158	99.4	96.5	100	1247.4	1019.3	1526.6	<8.0	38767
		PIII(M7)	160	159	99.4	96.6	100	6408.3	5459.7	7521.6	<8.0	67959
		PIII(M12)	151	151	100	97.6	100	2923.8	2511.1	3404.3	210	26849
		PIII(M24)	143	143	100	97.5	100	1574.9	1354.4	1831.4	193	12965
		PIII(M36)	139	139	100	97.4	100	1238.4	1060.5	1446.1	182	10346
		Total	1029	161	15.6	13.5	18	5.4	5.2	5.7	<8.0	502
		PII(M6)	1020	1018	99.8	99.3	100	698.9	655.4	745.2	<8.0	38767

		PIII(M7)	1021	1016	99.5	98.9	99.8	8698.2	8171.5	9259	<8.0	187703
		PIII(M12)	986	984	99.8	99.3	100	3224.9	3029.6	3432.8	<8.0	87534
		PIII(M24)	936	935	99.9	99.4	100	1588.1	1495.9	1685.9	<8.0	36310
		PIII(M36)	919	919	100	99.6	100	1260.6	1186.7	1339.1	25	23557
HAV	S-	PRE	748	0	0	0	0.5	4	4	4	<8.0	<8.0
		PII(M6)	736	41	5.6	4	7.5	4.4	4.2	4.5	<8.0	2929
		PIII(M7)	738	34	4.6	3.2	6.4	4.4	4.2	4.6	<8.0	21663
		PIII(M12)	717	30	4.2	2.8	5.9	4.3	4.2	4.4	<8.0	2032
		PIII(M24)	670	32	4.8	3.3	6.7	4.3	4.2	4.5	<8.0	339
		PIII(M36)	663	35	5.3	3.7	7.3	4.4	4.2	4.5	<8.0	286
	S+	PRE	146	146	100	97.5	100	29.4	24.7	35	8	1055
		PII(M6)	138	118	85.5	78.5	90.9	24.1	19.7	29.5	<8.0	714
		PIII(M7)	138	105	76.1	68.1	82.9	21.3	17.2	26.5	<8.0	640
		PIII(M12)	133	100	75.2	67	82.3	20	16.1	24.8	<8.0	664
		PIII(M24)	137	95	69.3	60.9	76.9	18.5	14.8	23	<8.0	1295
		PIII(M36)	126	87	69	60.2	77	17.5	13.9	22	<8.0	1388
	Total	PRE	894	146	16.3	14.0	18.9	5.5	5.2	5.9	<8.0	1055.0
		PII(M6)	874	159	18.2	15.7	20.9	5.7	5.4	6.1	<8.0	2929.0
		PIII(M7)	876	139	15.9	13.5	18.5	5.6	5.3	6.0	<8.0	21663.0
		PIII(M12)	850	130	15.3	12.9	17.9	5.4	5.1	5.8	<8.0	2032.0
		PIII(M24)	807	127	15.7	13.3	18.4	5.6	5.2	5.9	<8.0	1295.0
		PIII(M36)	789	122	15.5	13.0	18.2	5.4	5.1	5.8	<8.0	1388.0

HAV = Hepatitis A vaccine (three lots)

S- = seronegative subjects (antibody titer < 8 EL.U/ML) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 8 EL.U/ML) prior to vaccination

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with pre-vaccination results available

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

MIN/MAX = Minimum/Maximum

PRE = Pre-vaccination

PII(M6) = Post Dose II (Month 6)

PIII(M7) = Post Dose III (Month 7)

PIII(M12) = Post Dose III (Month 12)

PIII(M24) = Post Dose III (Month 24)

PIII(M36) = Post Dose III (Month 36)

**Table 10 Seropositivity rates and GMTs for anti-HPV-18 antibody titers (ATP cohort for immunogenicity)**

			≥ 7 EL.U/ml					GMT				
						95% CI			95% CI			
Group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV	S-	PRE	933	0	0	0	0.4	3.5	3.5	3.5	<7.0	<7.0
		PII(M6)	924	921	99.7	99.1	99.9	540.1	507.9	574.5	<7.0	23874.0
		PIII(M7)	924	919	99.5	98.7	99.8	4744.6	4454.1	5053.9	<7.0	142964.0
		PIII(M12)	895	895	100	99.6	100	1522.8	1431.7	1619.8	79	62477.0
		PIII(M24)	848	847	99.9	99.3	100	703.8	657.7	753.2	<7.0	30567.0

		PIII(M36)	835	835	100	99.6	100	534	498.6	572	28	20621.0
	S+	PRE	96	96	100	96.2	100	24.4	19.8	30.2	7	1397.0
		PII(M6)	96	95	99	94.3	100	892.5	704.2	1131.2	<7.0	30703.0
		PIII(M7)	96	96	100	96.2	100	4131.3	3539.2	4822.6	658.0	31432.0
		PIII(M12)	91	91	100	96	100	1505.7	1265.8	1791.1	241.0	18730.0
		PIII(M24)	88	88	100	95.9	100	742.9	616.6	895.1	148.0	16554.0
		PIII(M36)	85	85	100	95.8	100	577.5	471.2	707.7	124.0	12798.0
	Total	PRE	1029	96	9.3	7.6	11.3	4.2	4	4.4	<7.0	1397.0
		PII(M6)	1020	1016	99.6	99	99.9	566.3	533	601.7	<7.0	30703.0
		PIII(M7)	1020	1015	99.5	98.9	99.8	4683.2	4414.7	4967.9	<7.0	142964.0
		PIII(M12)	986	986	100	99.6	100	1521.3	1435.3	1612.4	79.0	62477.0
		PIII(M24)	936	935	99.9	99.4	100	707.4	663.7	754	<7.0	30567.0
		PIII(M36)	920	920	100	99.6	100	537.9	504	574.1	28	20621.0
HAV	S-	PRE	787	0	0	0	0.5	3.5	3.5	3.5	<7.0	<7.0
		PII(M6)	768	29	3.8	2.5	5.4	3.7	3.6	3.8	<7.0	4271.0
		PIII(M7)	769	31	4	2.8	5.7	3.8	3.6	3.9	<7.0	9564.0
		PIII(M12)	745	34	4.6	3.2	6.3	3.8	3.6	3.9	<7.0	4060.0
		PIII(M24)	695	35	5	3.5	6.9	3.8	3.7	3.9	<7.0	235.0
		PIII(M36)	689	31	4.5	3.1	6.3	3.7	3.6	3.8	<7.0	295.0
	S+	PRE	108	108	100	96.6	100	23.4	18.9	29.1	7.0	745.0
		PII(M6)	105	90	85.7	77.5	91.8	19.6	15.2	25.4	<7.0	1706.0
		PIII(M7)	105	90	85.7	77.5	91.8	20.8	16.2	26.8	<7.0	1363.0
		PIII(M12)	106	89	84	75.6	90.4	19.9	15.5	25.5	<7.0	822.0
		PIII(M24)	102	84	82.4	73.6	89.2	18.9	14.6	24.4	<7.0	722.0
		PIII(M36)	98	73	74.5	64.7	82.8	16.8	12.8	22.1	<7.0	467.0
	Total	PRE	895	108	12.1	10.0	14.4	4.4	4.2	4.6	<7.0	745.0
		PII(M6)	873	119	13.6	11.4	16.1	4.5	4.3	4.8	<7.0	4271.0
		PIII(M7)	874	121	13.8	11.6	16.3	4.6	4.4	4.9	<7.0	9564.0
		PIII(M12)	851	123	14.5	12.2	17.0	4.6	4.4	4.9	<7.0	4060.0
		PIII(M24)	797	119	14.9	12.5	17.6	4.6	4.4	4.9	<7.0	722.0
		PIII(M36)	787	104	13.2	10.9	15.8	4.5	4.3	4.8	<7.0	467.0

HAV = Hepatitis A vaccine (three lots)

S- = seronegative subjects (antibody titer < 8 EL.U/ML) prior to vaccination

S+ = seropositive subjects (antibody titer ≥ 8 EL.U/ML) prior to vaccination

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with pre-vaccination results available

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

MIN/MAX = Minimum/Maximum

PRE = Pre-vaccination

PII(M6) = Post Dose II (Month 6)

PIII(M7) = Post Dose III (Month 7)

PIII(M12) = Post Dose III (Month 12)

PIII(M24) = Post Dose III (Month 24)

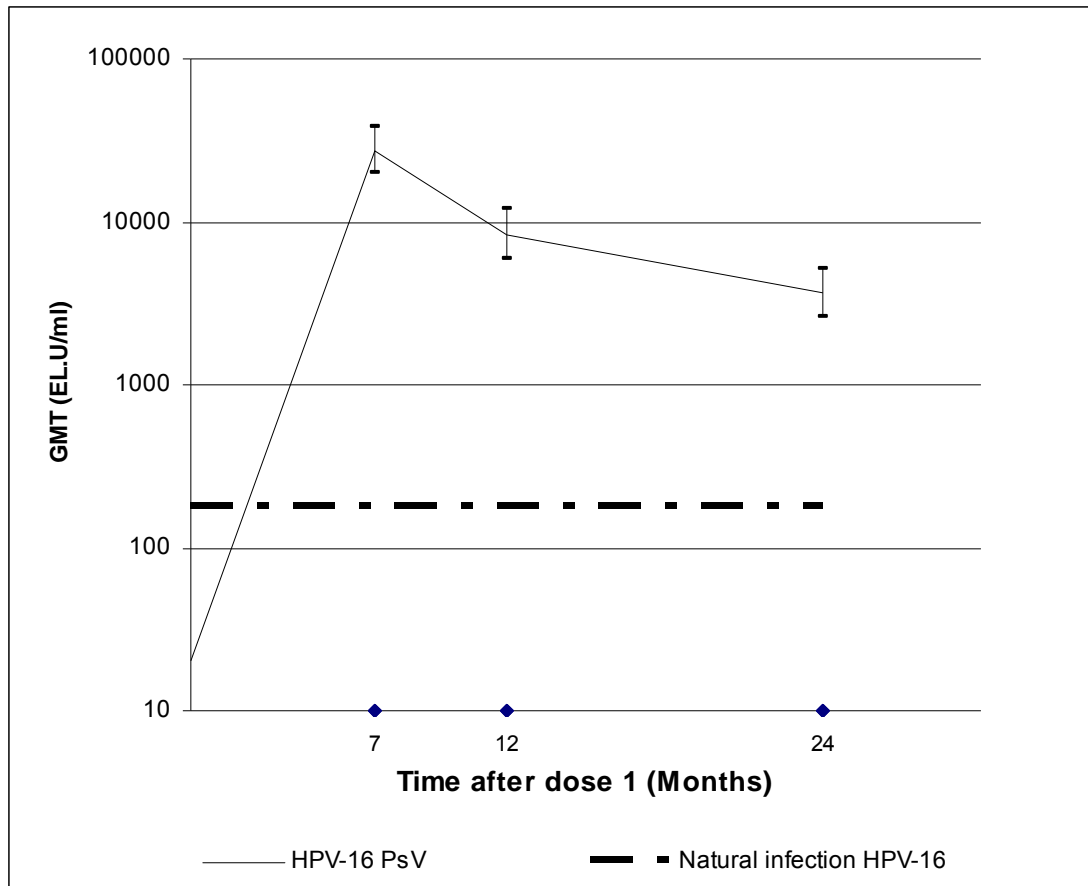
PIII(M36) = Post Dose III (Month 36)

#### Anti-HPV-16 (Figure 1) and anti-HPV-18 (Figure 2) PBNA:

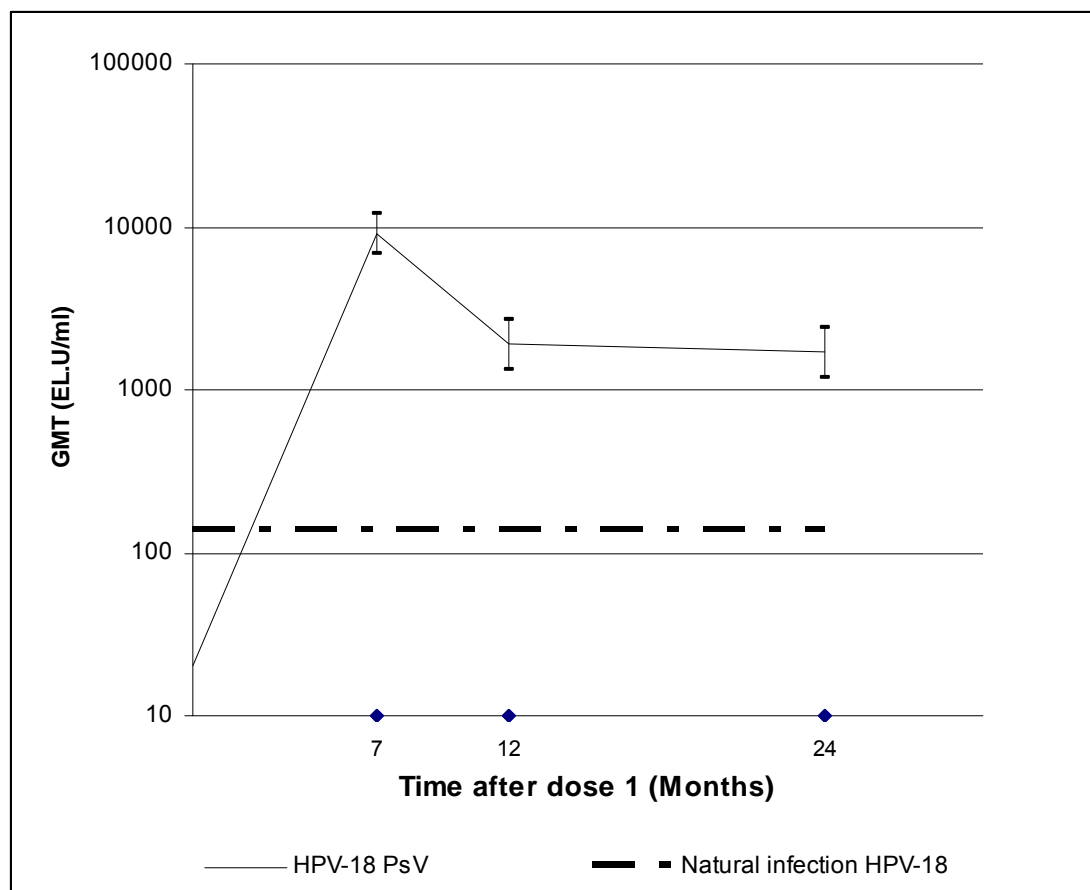
The results obtained by PBNA are similar to those obtained by ELISA. All evaluated subjects in the HPV group were seropositive for anti-HPV-16 and anti-HPV-18 neutralizing antibodies at Month 24, i.e. up to 18 months after completion of the full vaccination course. After a peak

response at Month 7, GMTs for anti-HPV-18 neutralizing antibodies already reached a plateau at Month 12, while GMTs for anti-HPV-16 neutralizing antibodies gradually declined up to Month 24 (with a smaller decline between the Month 12 and 24 timepoints). GMTs by PBNA were well above levels elicited after naturally acquired infection at each timepoint post-vaccination (20.3-fold higher for HPV-16 and 12.3-fold higher for HPV-18 at Month 24).

**Figure 1 Kinetics for anti-HPV-16 antibodies using PBNA in initially seronegative subjects with anti-HPV-16 PBNA results available at all timepoints (ATP cohort for immunogenicity - HPV group)**



**Figure 2 Kinetics for anti-HPV-18 antibodies using PBNA in initially seronegative subjects with anti-HPV-16 PBNA results available at all timepoints (ATP cohort for immunogenicity - HPV group)**



**Reviewer's comments:** I reproduced these two figures based on the information in the Clinical Study Report for Study HPV-008 dated February 2009.

### IV.3 Study HPV-007

One of the “other objectives” (other than the primary and secondary objectives) was to evaluate long-term vaccine immunogenicity (for all subjects by enzyme-linked immunosorbent assay [ELISA], and in a subset of subjects by V5/J4 monoclonal antibody inhibition tests and/or neutralizing assays).

#### Immunogenicity subset

In study HPV-001, a subset of 160 subjects was tested for anti-HPV-16 and anti-HPV-18 antibodies using V5/J4 monoclonal antibody inhibition enzyme immunoassays. This subset included 100 vaccinees and 50 placebo recipients (randomly selected) who received all three doses and had serum samples available for Visits 1, 4, and 8 (Months 0, 7, and 18) and 12 subjects having developed an HPV-16 or HPV-18 infection during the study (two subjects having a natural infection were part of the randomly selected subset).

In study HPV-007, subjects in the subset described above with serum samples available were tested by V5/J4 monoclonal antibodies.

## Immunogenicity Variables

At Months 0, 12, 24, and 36, 10 ml of whole blood (to provide a minimum of 3 ml of serum) was taken from each subject for serology testing. The serum samples were stored in a frozen condition and shipped to the laboratories at GSK Biologicals, Rixensart, Belgium. Serological assays were performed at GSK Biologicals' laboratories using standardized validated procedures with adequate controls.

Anti-HPV-16 and anti-HPV-18 ELISA testing was performed on serum from **all** subjects using a methodology developed by -----(b)(4)----- and modified by GSK Biologicals to evaluate antibody persistence.

The anti-HPV-16/18 immune response was also assessed using the pseudovirion neutralizing antibody assay. This testing was performed for the subset of subjects used for V5/J4 antibody testing with serum samples available and on an additional number of subjects randomly selected by the external statistician at Month 36 in order to meet the protocol-specified number of 100 vaccine recipients and at least 20 placebo recipients. In addition, analysis of neutralizing antibodies was performed for all subjects acquiring HPV-16 or HPV-18 infection during study HPV-007.

## Immunogenicity Results

Analysis of immunogenicity was performed on the ATP cohort for immunogenicity (primary analysis) and the Total cohort.

An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies at each time point is shown in [Table 11](#) (Table 46 in the Clinical Study Report for HPV-007) and [Table 12](#) (Table 47 in the Clinical Study Report for HPV-007), respectively. Up to 76 months following first vaccination in study HPV-001 (up to 70 months following completion of the full vaccination course), 98.6% or more of the vaccinated subjects remained seropositive for both HPV-16 and HPV-18 as measured by ELISA. GMT levels for both HPV-16 and HPV-18 reached a plateau during study HPV-007 at approximately one log below the peak response level observed at Month 7 (in study HPV-001) without substantial evidence of further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76).

**Table 11 Seropositivity rates and GMTs for anti-HPV-16 IgG antibody (ATP cohort for immunogenicity)**

			≥ 8 EL.U/mL				GMT				
					95% CI			95% CI			
Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Vaccine	PRE	301	18	6	3.6	9.3	4.3	4.2	4.4	<8.0	30
	PIII(M7)	301	301	100	98.8	100	4197.5	3766.1	4678.3	65	34561
	PIII(M12)	302	302	100	98.8	100	1241	1094.7	1406.8	70	25655
	PIII(M18)	300	299	99.7	98.2	100	737.8	651	836.2	<8.0	10228
	[M25-M32]	71	70	98.6	92.4	100	670.4	489.2	918.8	<8.0	9900
	[M33-M38]	172	171	99.4	96.8	100	454.7	381.7	541.6	<8.0	4974



	[M39-M44]	126	126	100	97.1	100	567.8	475.9	677.4	46	5264
	[M45-M50]	190	190	100	98.1	100	399.4	340.6	468.5	29	4562
	[M51-M56]	100	100	100	96.4	100	622.8	506.1	766.5	74	6137
	[M57-M62]	179	179	100	98	100	426.7	362	503	29	5479
	[M63-M68]	103	103	100	96.5	100	542.3	439.7	668.7	64	5659
	[M69-M74]	178	177	99.4	96.9	100	394.3	332	468.4	<8.0	4233
	[M75-M76]	52	52	100	93.2	100	463.6	360.8	595.5	89	4707
Placebo	PRE	5	0	0	0	52.2	4	4	4	<8.0	<8.0
	PIII(M7)	5	1	20	0.5	71.6	4.9	2.8	8.6	<8.0	11
	PIII(M12)	5	0	0	0	52.2	4	4	4	<8.0	<8.0
	PIII(M18)	5	0	0	0	52.2	4	4	4	<8.0	<8.0
	[M25-M32]	54	5	9.3	3.1	20.3	4.4	4	4.7	<8.0	13
	[M33-M38]	131	14	10.7	6	17.3	4.9	4.3	5.4	<8.0	405
	[M39-M44]	85	10	11.8	5.8	20.6	4.8	4.3	5.5	<8.0	125
	[M45-M50]	142	16	11.3	6.6	17.7	4.8	4.3	5.3	<8.0	151
	[M51-M56]	69	9	13	6.1	23.3	5.1	4.2	6.1	<8.0	677
	[M57-M62]	131	26	19.8	13.4	27.7	5.5	4.8	6.2	<8.0	181
	[M63-M68]	67	10	14.9	7.4	25.7	4.8	4.3	5.3	<8.0	21
	[M69-M74]	130	13	10	5.4	16.5	4.8	4.4	5.4	<8.0	72
	[M75-M76]	35	4	11.4	3.2	26.7	4.6	4	5.3	<8.0	17

Vaccine = HPV-16/18 L1/AS04; Placebo = Aluminum hydroxide

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

MIN/MAX = Minimum/Maximum

PRE = Pre-vaccination

PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)

[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)

[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)

[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)

[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)

[M75-M76] = Post Dose III (75<=Month<=76)

**Table 12 Seropositivity rates and GMTs for anti-HPV-18 IgG antibodies (ATP cohort for immunogenicity)**

			$\geq 7$ EL.U/mL				GMT				
					95% CI			95% CI			
Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Vaccine	PRE	301	30	10	6.8	13.9	3.9	3.8	4.1	<7.0	33
	PIII(M7)	300	300	100	98.8	100	3358	3041.8	3707	107	45888
	PIII(M12)	302	302	100	98.8	100	995.3	888.5	1115	91	30401
	PIII(M18)	300	299	99.7	98.2	100	591.9	524.7	667.8	<7.0	7518
	[M25-M32]	71	70	98.6	92.4	100	596.9	439.6	810.5	<7.0	12988
	[M33-M38]	172	171	99.4	96.8	100	378.6	320	447.9	<7.0	3711
	[M39-M44]	127	126	99.2	95.7	100	435.1	351.1	539	<7.0	11173
	[M45-M50]	190	190	100	98.1	100	297.5	254.4	348	22	5649
	[M51-M56]	100	100	100	96.4	100	454.9	370.8	558.1	23	8272
	[M57-M62]	179	179	100	98	100	322.5	274.9	378.4	23	4775

	[M63-M68]	103	103	100	96.5	100	359.9	295	439.2	24	6130
	[M69-M74]	178	177	99.4	96.9	100	305.3	258.1	361.1	<7.0	3415
	[M75-M76]	52	52	100	93.2	100	279.8	218	359.1	55	2408
Placebo	PRE	5	0	0	0	52.2	3.5	3.5	3.5	<7.0	<7.0
	PIII(M7)	5	1	20	0.5	71.6	4.1	2.6	6.5	<7.0	8
	PIII(M12)	5	0	0	0	52.2	3.5	3.5	3.5	<7.0	<7.0
	PIII(M18)	5	0	0	0	52.2	3.5	3.5	3.5	<7.0	<7.0
	[M25-M32]	54	4	7.4	2.1	17.9	3.9	3.5	4.3	<7.0	35
	[M33-M38]	131	16	12.2	7.1	19.1	4.1	3.8	4.5	<7.0	56
	[M39-M44]	87	15	17.2	10	26.8	4.6	4	5.4	<7.0	341
	[M45-M50]	142	19	13.4	8.3	20.1	4.2	3.8	4.5	<7.0	58
	[M51-M56]	68	13	19.1	10.6	30.5	4.7	3.8	5.6	<7.0	561
	[M57-M62]	131	16	12.2	7.1	19.1	4.2	3.8	4.5	<7.0	44
	[M63-M68]	66	10	15.2	7.5	26.1	4.3	3.7	4.9	<7.0	52
	[M69-M74]	131	19	14.5	9	21.7	4.5	4	5	<7.0	121
	[M75-M76]	35	5	14.3	4.8	30.3	4.3	3.6	5.2	<7.0	27

Vaccine = HPV-16/18 L1/AS04; Placebo = Aluminum hydroxide

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

MIN/MAX = Minimum/Maximum

PRE = Pre-vaccination

PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)

[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)

[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)

[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)

[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)

[M75-M76] = Post Dose III (75<=Month<=76)

#### IV.4 Immunogenicity Conclusions

The immunogenicity results of HPV-008 show that:

- A strong immune response was induced by the HPV vaccine compared to the immune response elicited after natural infection, with 99.4% or more of the vaccinated subjects remaining seropositive for anti-HPV-16 and anti-HPV-18 antibodies (by ELISA) up to 30 months after completion of the three-dose vaccination course.
- The antibody kinetics for HPV-16 and HPV-18 are similar to those observed in other HPV studies, i.e., a peak response at Month 7, followed by a gradual decline in GMTs until approximately Month 24, after which timepoint a plateau level is reached. Vaccine-induced GMTs were well above titers associated with clearance of natural infection when analyzed by ELISA and PBNA (neutralizing titers).

The immunogenicity results of HPV-007 show that:

- Up to 76 months following first vaccination in study HPV-001, 98.6% or more of the vaccinated subjects remained seropositive for both HPV-16 and HPV-18 as measured by ELISA. For both antigens, the GMTs reached a plateau during the HPV-007 study at approximately one log below the peak response level observed at Month 7 in the HPV-001 study, without substantial evidence of further decline between Month 18 and Month 76 post vaccination.
- Anti-HPV-16 and anti-HPV-18 antibody titers were well above the natural infection level (observed in study HPV-008) at each time point considered.
- No substantial effect of geographical region (North America and Brazil) on seropositivity rates or GMTs for anti-HPV-16 and anti-HPV-18 antibodies was observed during this study.

## V. REVIEW OF RESPONSES TO THE CR LETTER

### V.1 Introduction

The applicant's responses to the statistical related items in the FDA Complete Response letter have been reviewed and summarized in the following sections. Items 4 through 11 are related to efficacy and Items 2c(i) and 3 concern safety issues.

### V.2 Efficacy

4. In Study HPV-008, the primary endpoint is defined as "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 18 serostatus (by ELISA)." Results of the interim analysis demonstrated that vaccine efficacy against CIN2+ associated with HPV-18 did not reach statistical significance (VE = 83.3% [-78.8%, 99.9%], p=0.1249). Please comment and explain how the data from this interim efficacy analysis supports an indication for both HPV 16 and 18-related CIN 2+ and cervical cancer prevention.

Summary of Responses: Based on the results of HPV-008 interim analysis, the pre-specified primary composite endpoint of CIN2+ efficacy associated with HPV-16/18 was met.

***Reviewer's comments:*** *In the pivotal study HPV-008, the endpoint of prevention of CIN2+ lesions associated with HPV-18 was met in the final analysis.*

5. We would like to reiterate that CBER did not concur with the interim analysis success criterion of the lower 97.9% confidence limit excluding only zero. As communicated to you via fax (June 17, 2005) and confirmed in a telecon between Dr. Gopa Raychaudhuri and Ms. Sharon Shapowal (July 15, 2005), CBER did not concur with a proposal for an interim analysis for study HPV-008 in which the criterion for the lower bound of efficacy of 0%, and stated that it be substantially above 0% (e.g., 30%). In Amendment 151 (Serial 150) to IND -(b)(4)-, the proposed clinical plan for licensure in the US, a LB  $\geq 25\%$  was cited as the lower bound at the

time of the interim analysis, and this was also acknowledged within the BLA in Section 1.3.5 of the Clinical Overview (p.78). Please restate your conclusion based on a lower bound of the 97.9% CI as  $\geq 25\%$ .

**Summary of Response:** The applicant acknowledges the agreement reached with CBER regarding the success criterion for licensure in the United States at the time of the interim analysis, and the need for the lower bound of the 97.9% confidence interval around the point estimate of vaccine efficacy to be greater than 25%. The reviewer has, indeed, discovered a typographical error in the conclusion paragraph of m2.5 Clinical Overview of the original submission Section 6.11 that should be corrected to avoid misrepresentation of the result.

**Reviewer's comments:** *The response appears to be acceptable.*

6. Regarding the difference in the analysis populations at the interim analysis and at the time of final analysis, the efficacy data submitted to support licensure in the prevention against HPV 16 and 18 related CIN 2+ was based on an interim analysis in the Total Vaccinated Cohort-1. In the HPV-008 Study Report (Synopsis, page 2), it states: "Objective of the interim analysis: The current report describes the results of the interim analysis. For this analysis, efficacy objectives have been assessed post dose 1 in adolescent and young adult women who were DNA negative for the corresponding HPV type at Month 0 with normal or low-grade cytology at baseline." A different population, the According to Protocol Cohort (ATP cohort), in which subjects will be seronegative at baseline and PCR negative through Month 6, will be used to assess efficacy at the time of the final analysis. We have the following comments:

- a. Of the 23 cases of CIN 2+ used to provide demonstration of efficacy at the time of the interim analysis, 14 subjects became PCR positive for the relevant vaccine HPV type by Month 6 (including subjects 10076, 13452, 14290, 14386, 16973, 20287, 11942, 21724, 12104, 12692, 20838, 4249, 4451, 14079). These 14 cases counted at the time of the interim analysis should not be counted as cases at the time of the final analysis, given the different analysis populations. Please confirm.

**Summary of Response:** The applicant confirms that these 14 cases will not be included in the final According to Protocol analysis, since PCR positivity at month 6 for the HPV type detected in the lesion is a criterion which prevents inclusion in the ATP cohort. However, it should be noted that these cases will be included in the final analysis of the TVC-1 cohort.

**Reviewer's comments:** *The response appears to be acceptable.*

- b. The primary analysis of vaccine efficacy against HPV 16 or 18 related CIN 2+ at the time of the interim analysis counted cases after dose 1. The indication for vaccine administration includes three doses of vaccine at 0, 1, and 6 months. The time to development of the 23 endpoint cases of CIN 2+ ranged from 8 months to 29 months, with a mean time to event of 15.9 months (median: 14 months), which is after administration of dose 3. (From the "n" doses dataset for Study HPV-008, another subject, #1298, received 2 doses of Havrix® prior to endpoint. All other subjects who developed a case counted as an endpoint received 3 doses.) Please explain how the

difference in the population assessed at the time of interim analysis and final analysis will be reconciled with the recommendation for three doses of vaccine.

**Summary of Response:** Studies which have evaluated the immunogenicity profile of *Cervarix* have demonstrated that peak immune responses are generated after completion of the 3-dose series. The administration of a third dose at month 6 has been shown to boost HPV-16 and HPV-18 responses several fold beyond levels measured after dose 2.

It should be noted that a final analysis was conducted in the TVC-1 cohort. This analysis, in conjunction with the final ATP evaluation, provided important supportive data that helps evaluate the impact of exclusion of subjects who have not received vaccine according to the protocol-specified requirements.

**Reviewer's comments:** *The response appears to be acceptable.*

- c. Since 22/23 of the subjects who developed a CIN 2+ endpoint had received three doses, and the time to development of a case varies from 8 months to 29 months, i.e., after the time of the third dose, the data do not provide evidence that the vaccine has an early onset of effect. Please discuss.

**Summary of Response:** Evidence of an early onset of vaccine effect was not directly assessed in the interim analysis of HPV-008. However, of the 23 cases of CIN2+ associated with HPV-16/18 included in the interim analysis, 14 cases occurred in women who were found to be infected at the month 6 visit with the corresponding type subsequently found in the lesion. Since the third vaccine dose is administered at the month 6 visit, these cases were associated with infections which developed prior to completion of the 3 dose immunization series. All 14 cases occurred in women in the control group. Therefore, the distribution of CIN2+ cases arising in women who acquired their infections prior to receiving all three doses of vaccine (i.e., 0 cases in *Cervarix* group vs. 14 cases in the control group) strongly suggests an early onset of effect.

**Reviewer's comments:** *The response appears to be acceptable.*

7. In study HPV-008, for the evaluation 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), there are 14 different secondary analyses and no adjustment for alpha has been considered. It is possible that a correlation between prevention of persistent and incident infection with CIN 2+ prevention may be demonstrated in the future, but the current data are not indicative of this. Furthermore, the current analyses related to persistent and incident infections lack adjustment and introduce considerable Type I error probability. The same comment applies to the evaluation of histopathologically-confirmed CIN1+ (or CIN2+) associated with the oncogenic HPV types detected within the lesional component of the cervical tissue specimen. Please comment.

**Summary of Response:** The statistical approach used by the applicant in the interim analysis of HPV-008 was designed to control Type I error by: 1) including an Alpha adjustment; 2) applying a sequential approach to secondary endpoint evaluations; and 3) only considering

relevant individual type analyses for endpoints where the composite evaluation was met and consistent results were found. With respect to evaluation of the vaccine effect on each individual oncogenic HPV type, the approach was carefully undertaken in order to minimize the risk of false findings due to multiplicity.

**Reviewer's comments:** 1) The Alpha adjustment included was related to the interim analysis, not for tests of multiple HPV types; 2) The evaluation of histopathologically-confirmed CIN2+ associated with the oncogenic HPV types (14 types) was not adjusted for multiplicity (Table 43, page 270 in HPV-008 Final Report). Vaccine efficacy of CIN 2+ associated with HPV-31 may be the only type (other than HPV-16 and -18) which showed possible statistically significant result. However, the clinical meaning of this result needs to be judged by the clinical reviewer, Dr. Nancy Miller.

8. In the Clinical Overview on p.41, you state that interim safety data and immune responses in women > 26 years of age provide evidence that Cervarix protects against CIN 2+ associated with HPV 16 or 18 in this older age group. Given the absence of efficacy data in this population against development of CIN 2+, the likelihood that older women are sexually experienced, the type-specific lack of efficacy in females with pre-existing HPV infections, and the lack of information from study 015 regarding the proportion of women who were non naïve at baseline, it remains unclear if Cervarix will prevent HPV 16 or 18 related CIN 2+ in this older age group. Please comment.

Summary of Response: The applicant believes that it is important for women above 25 years of age to have access to HPV-16/18 vaccination. In summary:

- Anti-HPV antibodies are only detected in approximately 50% of women who are naturally infected with HPV. Seropositivity following natural infection does not appear to provide protection against re-infection (data source: HPV-008).
- Baseline characteristics prior to vaccination with respect to HPV-16/18 seropositivity and HPV-16/18 DNA positivity show that the vast majority of women, including those over 25 years of age, are uninfected and remain at risk for new infections and downstream consequences. Regardless of age, only 0.1- 0.5% of women are DNA positive for both HPV-16 and HPV-18. (data source: HPV-008, HPV-014 and HPV-015).
- The vaccine is efficacious, regardless of the initial serological status. In addition, in subjects with a past (seropositive) or current (HPV DNA positive) infection with either HPV-16 or HPV-18, the vaccine remains efficacious for the other vaccine type (data source: HPV-008). These women could still benefit from vaccination since they will be protected against the other type.
- Importantly, antibody levels induced in women 26-55 years of age at Months 7, 12 and 18 were higher than or similar to the “plateau” titers measured in the efficacy study HPV-007. Therefore, they are expected to be in a range that correlates with protection. At Month 24, antibody-titers for both anti-HPV-16 and anti-HPV-18 remained at least 8-fold higher than the natural infection titers defined in the HPV-008 study (data source: HPV-014).
- The majority of subjects who had cervical secretion samples evaluated at Month 18 had detectable antibodies for both antigens, indicating transudation of the antibodies from the

serum to the cervical epithelium. Positive correlations were observed between the antibody response elicited by the vaccine in serum and the antibody response elicited in cervical secretions at Month 18 and Month 24 (data source: HPV-014).

- The vaccine has been shown to be safe and generally well-tolerated. There is no evidence that cervical disease is enhanced in women with histopathological lesions caused by HPV-16/18 infections present at the time of vaccination.

**Reviewer's comments:** *The responses are based on results of HPV-008 and HPV-014. HPV-008 is a study focusing on women between 10 and 25 years of age and HPV-014 is a long-term, open-label, age-stratified follow-up study of the immunogenicity and safety. Given that the natural history of HPV infection and the pathogenesis of cervical cancer are different between the younger (10-25 years of age) and the older women (above 25 years of age), it is necessary to have a well-designed clinical study to evaluate vaccine efficacy against CIN 2+ associated with HPV 16 or 18 in this older age group, should an indication related to this population be proposed in the future.*

9. Since all HPV-001 and HPV-007 combined analyses were descriptive, CBER views them as exploratory and unlikely to support label claims. Please comment.

**Summary of Response:** While the analyses of the histopathological (CIN2+, CIN1+) and persistent infection endpoints derived from the combined data were to be descriptive, they were important for answering questions relative to vaccine performance.

**Reviewer's comments:** *I view the HPV-001 and HPV-007 combined descriptive analyses as exploratory.*

10. We note that no correlation between immunogenicity and vaccine efficacy has been identified in studies HPV-008 and HPV-001/007. In particular, it is important to investigate the immunogenicity information of those CIN2+ cases associated with HPV-16/18. Please provide immunological data for CIN 2+ cases in the study group that received Cervarix.

**Summary of Response:** Given the small number (n=2) of *Cervarix* recipients who developed CIN2+ lesions in whom vaccine immunogenicity can be assessed and the likelihood that the lesions detected were not attributable to vaccine HPV types, no conclusions can be made about correlations between immunogenicity and vaccine efficacy at this time.

**Reviewer's comments:** *I acknowledge that due to the small number of cases, no conclusion can be made about correlations between immunogenicity and vaccine efficacy.*

11. Results of Studies HPV-012 and HPV-013 Ext. show that the immune response in 10-14 year old girls was sustained up to 18 months following vaccination. Please provide a plan of assessing the immune response beyond 18 months after vaccination in this age group. Please provide similar information for women 26 years of age and above.

**Summary of Response:** The immunogenicity assessment of 10-14 year old girls is planned through month 48, and extension protocols have been written, accordingly. We confirm that

long-term immunogenicity data for girls and adolescents will derive from the extension of studies HPV-012 and HPV-013. The scheduled timepoints for assessment of immunogenicity include month 18 (within BLA), month 24, month 36 and month 48. The same schedule of assessment and the same length of observation (up to month 48) is planned for the subpopulation of women >26 years of age, enrolled in the long-term extensions to study HPV-014.

**Reviewer's comments:** *The response appears to be acceptable.*

### **V.3 Safety**

2c. Please provide an updated table of pregnancy outcomes through September 30, 2007, including information from studies 001/007, 008, 009, 012, 013, 014, 015, 016. Specifically we have the following comments and requests:

- i. The reported rates of spontaneous abortion are higher in the HPV vaccine group as compared to the HAV (control) group in Study HPV-008. You claim that the rates in both groups are lower than those reported in US epidemiological studies of spontaneous fetal losses from recognized pregnancies (13-16%). It should be noted that "fetal loss" includes live births, stillbirths, spontaneous abortions (including hydatidiform mole), and ectopic pregnancies. As shown in one of the publications which you cited (Goldhaber, 1991), "Omitting ectopic pregnancies decreased the estimate (rate of spontaneous abortions) to 11.9%." Therefore, the reported rates of spontaneous abortion may in fact be similar or even higher than those in US epidemiological studies.

Summary of Response: The applicant provided an updated analysis. The analysis extends the evaluation to a more recent data lock point. In addition, a table of the articles showing spontaneous abortion frequencies in the US was presented. In conclusion, significant variability exists in the reported rates for spontaneous abortion in the US; from 9.1% to 45.5% (including Goldhaber's study).

**Reviewer's comments:** *A detailed review of pregnancy issues is included in Section III.2, III.3, and III.4 (page 27).*

3. Regarding the meta-analysis of results for MPL-containing products, results of the statistical test for homogeneity of the common relative risks of Grave's disease tend to be statistically significant in both Level 2 and Level 3 analyses. This evidence of lack of homogeneity of relative risks across studies suggests that the overall summary analysis results may be subject to bias. Thus, further careful review of the data for each individual study regarding the rates of Grave's disease may be warranted. Please comment.

Summary of Response: Since the homogeneity of the relative risks across studies with respect to Graves disease has been called into question, the Company has calculated, as requested, the percentage of subjects reporting the occurrence of Graves disease and the estimated relative risks per study, for level 2. For Study HPV-008, five cases were reported: four in the MPL group and one in the non-MPL group, with an estimated relative risk of 4.00 (95% CI: 0.40; 197.11), For



Study HPV-009, one case was reported in the MPL group. No estimated relative risk could be calculated. For Study HPV-015, one case was reported in the non-MPL group, with an estimated relative risk of 0.00 (95% CI: 0.00; 38.86). For Study HSV-016, two cases were reported in the non-MPL group, with an estimated relative risk of 0.00 (95% CI: 0.00; 2.76). For Study HSV-039, 1 case was reported in the MPL group. No relative risk could be calculated.

***Reviewer's comments:** Five cases were reported in Study HPV-008, with four in the MPL group and one in the non-MPL group. Although the number of reported cases is small, it is up to Dr. Nancy Miller's judgment as to whether this finding for Graves disease should be considered a signal.*

## **VI. COMMENTS TO THE REVIEW COMMITTEE**

- In Study HPV-008, the virological (incident, 6-month and 12-month persistent infection) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy; however, the clinical meaningfulness of these findings needs to be assessed by the clinical reviewer, Dr. Nancy Miller;
- As to the issues that the candidate vaccine reduced persistent infection and precancerous lesions or AIS caused by oncogenic HPV types other than HPV-16 and HPV-18, HPV-31 may be the only type that reached statistical significance if an adequate Type I error adjustment had been performed. The clinical meaningfulness of these findings is subject to the clinical reviewer's judgment.
- Although the applicant states "Evaluation of all pregnancy outcomes did not show any clinically meaningful differences between the groups," the clinical relevance of this finding should be determined by the clinical reviewer, Dr. Nancy Miller.

## **VII. COMMENTS TO THE APPLICANT**

- (Efficacy in HVP-008): Since the evaluation of histopathologically-confirmed CIN2+ associated with the oncogenic HPV types (14 types) was not adjusted for multiplicity (Table 43, page 270 in HPV-008 Final Report), the findings that the candidate vaccine reduced persistent infection and precancerous lesions or AIS caused by oncogenic HPV types other than HPV-16 and HPV-18 are not strictly statistically valid. HPV-31 may be the only type that would reach statistical significance if an adequate Type I error adjustment were performed. Moreover, the clinical meaningfulness of these findings is subject to the clinical reviewer's judgment.
- (Response to CR Item 8): The responses are based on results of HPV-008 and HPV-014. HPV-008 is a study focusing on women between 10 and 25 years of age, and HPV-014 is a long-term, open-label, age-stratified follow-up study of the immunogenicity and safety. Given that the natural history of HPV infection and the pathogenesis of cervical cancer are different between the younger (10-25 years of age) and the older women (above 25 years of age), it is necessary to have a well-designed clinical study to evaluate vaccine efficacy against CIN 2+ associated with HPV 16 or 18 in this older age group should an indication related to this population be proposed in the future.

## **VIII. REVIEWER'S RECOMMENDATION**

Based on data presented in Study HPV-008, the primary endpoint of the study, prevention of CIN2+ lesions associated with HPV-16 and/or HPV-18 (HPV-16/18), was met. The secondary histopathological (CIN3+, CIN1+, ASC-US+, and VIN/VaIN1+) efficacy endpoints associated with HPV-16/18 were statistically significant in the ATP cohort for efficacy in subjects who were seronegative at baseline and HPV DNA negative at baseline and Month 6. The proposed indications related to the above endpoints may be granted.

Although the applicant states "Evaluation of all pregnancy outcomes did not show any clinically meaningful differences between the groups," the clinical relevance of the unbalanced incidence rates of spontaneous abortion between the vaccine and the control groups in HPV-008 should be determined by the clinical reviewer, Dr. Nancy Miller