FDA Briefing Document

Vaccines & Related Biological Products Advisory Committee Meeting

September 9, 2009

Cervarix™
GlaxoSmithKline Biologicals

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OVRR/CBER/FDA

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Product: Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant
Trade Name: Cervarix™
Product Formulation: Each 0.5 mL dose of the vaccine contains:

20 mcg of HPV 16 L1 protein
20 mcg of HPV 18 L1 protein
500 mcg aluminum hydroxide
50 mcg 3-O-fesacyl-4'-monophosphoryl lipid A (MPL)
0.624 mg sodium dihydrogen phosphate dihydrate as buffer

Applicant: GlaxoSmithKline Biologicals (GSK)
Proposed Indications from the Applicant: Prevention of cervical cancer (squamous cell carcinoma and adenocarcinoma) by protecting against the following precancerous or dysplastic lesions and infections caused by oncogenic human papillomaviruses (including types 16 and 18 and some non-vaccine HPV 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
- incident Infection

Indications proposed by CBER: CERVARIX™ is a vaccine indicated in girls and women 10-25 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 16 and 18 included in the vaccine:

- Cervical cancer
- Cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1

Dosage Form and Routes of Administration: The vaccine is administered by intramuscular injection as a three dose series at 0, 1, and 6 months. It will be supplied in 0.5 mL single dose vials and prefilled -----(b)(4)---- syringes.

EXECUTIVE SUMMARY

Cervarix™ is a non-infectious, recombinant vaccine which contains Virus Like Particles (VLPs) of the L1 capsid proteins of HPV 16 and 18. It is adjuvanted with aluminum hydroxide and monophosphoryl lipid A. The proposed indication includes prevention of cervical cancer and precancerous lesions (CIN 1,2,3 and AIS) associated with HPV 16 and 18. Data from 13 studies involving ~30,000 females 10-55 years of age was submitted to the Biologics Licensing Application (BLA) in support of licensure.

The pivotal efficacy study, HPV-008, was a randomized (1:1), controlled, double blind trial which recruited 18,000+ women, regardless of cytology status or evidence of HPV exposure, to compare Cervarix to active control (Havrix) for the prevention of CIN2+. In the According to Protocol (ATP) population, efficacy against HPV 16 and 18 associated CIN2+ was 92.9%, with 96.1%CI (79.9, 98.3). To estimate impact in the general population, an intent-to-treat analysis was performed in the Total Vaccinated Cohort (TVC), in which 26% of subjects were seropositive and/or PCR positive to HPV 16 and/or 18; vaccine efficacy against CIN2+ regardless of HPV type association was 30.4%, with 96.1%CI (16.4, 42.1).

Prophylactic efficacy in an HPV naïve population (defined as PCR negative for all oncogenic HPV, seronegative for HPV 16/18, and cytology normal at baseline) was evaluated in the phase IIB study, HPV 001/007. Although the study was not powered for CIN2+, secondary analysis for

this endpoint generated a point estimate of efficacy of 100%, with 95%CI (19.7, 100); and among the subset of subjects followed for 6 years, 0 cases of HPV 16/18 persistent infection and 0 cases of HPV 16/18 associated CIN2+ occurred in the Cervarix arm.

The potential for cross protection against non-vaccine HPV types was analyzed in multiple ways. In the ATP cohort from HPV-008, efficacy against 6-month persistent infection was 78.7%, 45.7%, and 75.7% for types 31, 33, and 45, respectively, with 96.1% CI's >20% in each case. On the other hand, efficacy against CIN2+ associated with any oncogenic type other than 16 or 18 was relatively modest: 37.4% with 96.1%CI (7.4, 58.2). In addition, in CBER's analysis of each individual oncogenic type controlling for Type 1 error, only 31 reached statistical significance for prevention of CIN2+.

Immunogenicity was measured by ELISA titers, which were shown to correlate well with pseudoneutralization assay titers. Immune responses to Cervarix were robust and consistent. In each study, GMT's in the Cervarix group were considerably higher than those in subjects with history of natural infection. Seroconversion rates (SCR) in study HPV-008 were 99.5% at 1 month post-dose 3. And SCR's remained high (~98%) in the subset of subjects followed to 76 months in HPV-001/007.

Because the incidence of HPV-related genital lesions is very low before the onset of sexual relations, a placebo-controlled efficacy trial in subjects <16 years of age would be impractical. CBER has therefore accepted immunogenicity bridging studies as a reasonable approach to inferring protection in this age group. In two Phase II studies (012 and 013), antibody titers against both VLP types in 10-15 year old subjects were non-infererior to those in 15-26 year old subjects.

Cervarix is adjuvanted with ASO4, a combination of aluminum hydroxide ($AlOH_3$) and monophosphoryl lipid A (MPL). If approved, Cervarix would be the first vaccine licensed in the U.S. which contains MPL as a component of the adjuvant. In preclinical studies and phase IIa trials, the sponsor demonstrated higher initial titers with the addition of MPL over $AlOH_3$ alone. In subjects followed to 4 years, the difference persisted with statistically significantly higher GMT's (by most measures) in the ASO4 group. No correlate of protection has yet been established for prevention of HPV infection and disease, primarily because the low number of cases among vaccinees (with either HPV vaccine) prevents meaningful analysis of a possible correlation between vaccine failure and vaccine-induced anti-HPV titers. Therefore, the clinical significance of higher titers demonstrated with ASO4 is not yet clear.

Safety data from pivotal study HPV-008 were reviewed in depth by CBER clinical and statistical reviewers. The overall rate of AE's was somewhat higher in the Cervarix group compared with the Havrix group: 85.4% versus 74.6%, respectively. This was driven largely by higher rates of injection-site symptoms in the Cervarix versus Havrix groups. Analyses of systemic AE's, overall and by system organ class (SOC), were unremarkable. Similar percentages of subjects discontinued due to AE's. The number of SAE's and the number of deaths were similar in each group, and no patterns indicating a potential safety signal were discernible among the serious adverse outcomes.

One exception in the HPV-008 safety data was the finding of a higher rate of spontaneous abortions in the Cervarix group compared with Havrix: 11.6% versus 5%, respectively. A number of possible confounding variables were identified, including inconsistencies in reporting rates by country. In addition, the imbalance did not persist in an analysis of the entire study period in the pooled safety dataset. An independent statistical review requested by the DSMB

concluded that the data do not establish a causal relationship, but they are insufficient to rule out a small effect in pregnancies conceived in the 3 months immediately after vaccination.

The pooled safety database initially submitted to the BLA includes ~30,000 females 10-25 years of age, of which ~16,000 received at least one dose of Cervarix. Analyses of these data generally mirror what was found in the HPV-008 dataset.

There were, however, numerical imbalances in musculoskeletal and neuroinflammatory events of potential autoimmune etiology in the pooled safety dataset. The need to address this potential safety signal was one of the primary items communicated to the sponsor by CBER in December 2007. With the addition of close-out data from several studies, CBER re-analyzed the data and concluded that the differences between Cervarix and the pooled control group were not statistically significant. The sponsor convened external expert panels of rheumatologists and neurologists. In addition, the sponsor performed a meta-analysis that included clinical trials involving their other vaccines (HBV and HSV) with ASO4 adjuvant. CBER consulted an outside rheumatologist. The conclusion in the case of each of these efforts was that the data are not sufficient to establish a link.

The FDA is convening the Vaccines and Releated Biological Products Advisory committee to discuss whether the data submitted in the BLA support the safety and efficacy of Cervarix for prevention of HPV-related disease. Other items on which CBER will be seeking input include:

- the assessment of the safety data, specifically with regard to pregnancy outcomes and potential autoimmune associated event signaling
- data on cross-protection and the potential impact that may accrue from prevention of persistent infection with non-vaccine types
- use of persistent infection as a clinical study endpoint
- recommendations will be solicited regarding the proposed pharmacovigilance plan, particularly the approach to pregnancy outcome surveillance

INTRODUCTION AND BACKGROUND

Genital HPV is the most common sexually transmitted disease in the United States, and the Centers for Disease Control and Prevention (CDC) estimates that over 6 million people are infected each year.[1] There are > 100 HPV types identified, and approximately 40 HPV types infect the human genital tract. Most of these infections are self-limited, although certain high-risk HPV types are known to be carcinogenic. HPV-16 (alpha-9) and HPV-18 (alpha-7) were classified as cervical carcinogens by the World Health Organization International Agency for Research and Cancer in 1995, and HPV 31 and HPV 33 (alpha-9) were categorized as probably carcinogenic.[2,3] HPV 16 is considered a very efficient carcinogen, and is associated with approximately 55% of cervical cancers globally. HPV 18 is another important oncogenic HPV type and is associated with adenocarcinoma and another app. 16% of cervical cancers. Other oncogenic HPV types include HPV-31, 33, 39, 45, 51, 52, 56, 58, and 59, and account for a lower proportion of cervical cancers. The American Cancer Society estimates that approximately 11,270 cases of invasive cervical cancer will be diagnosed in the United States in 2009, and that approximately 4070 women will die from the disease. In the United States and other developed countries, the number of cases of cervical cancer and number of deaths from cervical cancer has

[1] CDC. Quadrivalent Human Papillomavirus Vaccine, Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007; 56 (RR02):1-24.
[2] Schiffman M et al. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. Infectious Agents and Cancer 2009; 4:8
[3] Schiffman M et al. Human papillomavirus and cervical cancer, The Lancet 2007; 370 (9590): 890-907

decreased significantly, and is largely the result of women getting regular Pap tests.[4] Worldwide, the World Health Organization (WHO) indicates that cervical cancer is the second most common cause of female cancer mortality, with 288,000 deaths yearly. The WHO estimates that approximately 510,000 cases of cervical cancer are reported each year, with 80% of cases in developing countries.[5]

Endpoint for demonstrating efficacy

In November 2001, the Vaccines and Related Biological Products Advisory Committee considered appropriate endpoints for licensure of HPV vaccines and determined that given standard of care in developed countries, CIN 2/3 and AIS or worse associated with vaccine HPV types could be considered a valid surrogate endpoint for cervical cancer. Thus, the primary efficacy endpoint for study HPV-008 was the prevention of CIN 2+ associated with the relevant vaccine HPV type for which the subject was naïve at baseline. Persistent infection with an oncogenic HPV type is also known to be associated with development of cervical cancer, although the specific duration of infection associated with oncogenesis has not been defined for the different oncogenic HPV types.

Vaccine Manufacture

The HPV-16/18 L1 VLP AS04 vaccine is manufactured through recombinant DNA technology using the baculovirus expression system. ----------(b)(4)----------.

AS04 Adjuvant

AS04, which contains aluminum hydroxide ($Al(OH)_3$) and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL), was included as an adjuvant in Cervarix™ to enhance the immune response to the VLPs for HPV-16 and HPV-18. MPL is derived from cell wall lipopolysaccharide (LPS) of the Gram-negative *Salmonella minnesota* R595 strain, but demonstrates greatly reduced toxicity and pyrogenicity compared to the parent LPS molecule. GSK and many research groups are currently studying the mechanisms of action of MPL and $Al(OH)_3$. MPL is a stimulator of the innate immune system, thought to act primarily as a Type 4 Toll-like Receptor (TLR4) agonist. (TLRs constitute a family of receptors that recognize a broad range of microbial stimuli. Distinct TLRs recognize different microbial stimuli and in humans, distinct subsets of innate immune cells express different TLRs.) GSK has data to suggest that like $Al(OH)_3$, MPL acts locally at the site of injection to target antigen presenting cells (APCs) and AS04 appears to enhance activation of APCs and migration into the local draining lymph node. Other data suggest that as compared to LPS, MPL results in a lower induction of proinflammatory cytokines at the injection site.

REGULATORY BACKGROUND

The first U.S. licensed preventive HPV vaccine was Gardasil®, a recombinant VLP vaccine which contains the L1 capsid proteins of HPV 6, 11, 16, and 18. This vaccine was licensed (June 8, 2009) for use in females 9-26 years of age to prevent cervical, vaginal and vulvar cancer caused by HPV types 16 and 18; genital warts (condyloma acuminata) caused by HPV types 6

[4] http://www.cdc.gov/cancer/cervical/statistics/

[5] http://www.who.int/vaccine_research/diseases/hpv/en/

and 11; and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18: CIN grade 2/3 and cervical adenocarcinoma in situ; CIN grade 1; Vulvar Intraepithelial Neoplasia grade 2 and grade 3; and Vaginal Intraepithelial Neoplasia grade 2 and grade 3.

Cervarix™ has been investigated under a U.S. Investigational New Drug (IND) application to CBER beginning in September 1998. Since then, studies have been conducted both under IND as well as in non-IND studies outside the U.S., and these study reports were submitted to the Biologics License Application (BLA) in support of licensing the product. GlaxoSmithKline submitted a BLA for Cervarix™ on March 29, 2007. In review of this original submission, CBER assessed that additional efficacy and safety data were required in order for CBER to satisfactorily complete their review. A Complete Response letter was sent to GSK on 12/14/09. GSK provided satisfactory responses to the comments, and all requests had been completed as of the re-submission date of 3/27/09.

Table 1- Regulatory Background Information [CBER generated]

Date	Action
7/98	Pre-IND meeting
9/98	Original IND Submission
11/01	VRBPAC meeting to discuss Endpoints for Phase 3 trials
2/04	End of Phase 2 meeting
5/06	Pre-BLA Meeting
3/07	Submission of BLA
7/10/07	Request for safety meta-analysis for all MPL products
12/14/07	CR Letter sent
6/26/08	Meeting with CBER and GSK re:discussion of safety and proposal for final efficacy 008
10/4/08	Meeting with CBER and GSK re: discussion re: AS04 and MPL
3/29/09	Completion of responses to CR letter
6/22/09	Request for NCI analysis of spontaneous abortions in HPV-008 and HPV-009
7/13/09	First labeling comments sent to GSK
7/20/09	Second labeling comments sent to GSK
9/9/09	VRBPAC meeting to discuss Cervarix™

CLINICAL OVERVIEW

A table of the clinical studies which were reviewed in the Cervarix™ BLA is provided below.

Table 2 - Clinical Studies Reviewed in Cervarix™ BLA

Study Number	Vaccine HPV Type	Phase	Endpoint	Total sample size: Cervarix™ [C]/Control	Geographic Distribution of Study Populations	Dates conducted
002	16, 18 & 16/18	I	S and I for monovalent and bivalent vaccine in naïve females 18-30 years of age	N=49	United States	2/99-7/99
003*	16/18 (includes non-naïve)	I/IIa	S and I for bivalent vaccine in non-naïve females 18-30 years of age	N=61 (31 C/30 AlOH3)	United States	11/99-6/01
004*	16/18 (no adjuvant, AlOH3, AS04)	I/IIa	S and I for adjuvanted and unadjuvanted products in naïve females 18-30 year s of age	N=60	United States	10/00-12/01 + 4 year extension for subgroup
005*	16/18 (dose	IIa	S and I for different VLP doses adjuvanted with	N=209	United States	10/99-5/01 + 4 year extension for

	ranging)		AS04 or Al(OH)3 in naïve females 18-30 years of age			subgroup
001*	16/18	IIb	E (incident infection), I, S - RCT in naïve* females 15-25 years of age (Cervarix™ compared to Al(OH)3 [18 months initial with extension to 27 months]	N=1113 (560 C/553 AlOH3)	Brazil, Canada and United States	1/01-4/03
007*	16/18	IIb	Extension study of HPV-001 in subgroup to follow E, I and S [follow-up up for additional 3 years]	N=776 (extension of study HPV-001: 393C/383 AlOH3)	Brazil, Canada and United States	11/03-7/05
008*	16/18	III	E, I, and S RCT study (CIN2+ related to HPV 16/18) in females 15-25 years of age (naïve and non-naïve) compared to Havrix	N=18644 (9319C/9325 Havrix)	Asia, Europe, North Americas, South America	5/04-ongoing (final analysis event driven with continued follow-up of subjects to 4 years]
009*†	16/18	III	E, I and S RCT study (CIN2+ related to HPV 16/18) in females 15-25 years of age (naïve and non-naïve)	N=7466	Costa Rica	Approximately 7/04 - ongoing
012	16/18	III	I and S uncontrolled study to compare immune responses in different age groups and lot consistency for vaccine produced by different methods	N=770 (lot consistency) (158 in 10-14 yo ♀ and 612 in 15-25 yo ♀)	Europe	9/04-7/05 (+12 months additional data provided to date)
013*	16/18 (10-14 year old girls)	III	I and S RCT in females 10-14 years of age (Cervarix™ compared to Havrix)	N=2067 (1035C/1032 Havrix)	Asia, Australia, Europe	6/04-8/05 (+ 12 months additional data provided to date)
014	16/18 (15-55 year old ♀)	III	I and S uncontrolled study to compare immune responses in females 25-55 years of age to those 15-25 years of age	N=666 (229 in 15-25 yo♀, 226 in 26-45 yo ♀, and 211 in 45-55 yo ♀)	Europe	10/04-7/05 (+12 months additional data provided to date)
015*†	16/18 (26-55 year old ♀)	III	E, I, and S RCT study (Persisent infection and CIN1+) in women >25 years of age as compared to Al(OH)3	N=5751 (2880C/2871 AlOH3)	Asia, Australia, Europe, North and South America	2/06-ongoing
016	16/18	III	I and S study for lot consistency in 18-25 year old females	N=798 (lot consistency)	Europe	10/05-9/06

S=Safety; I=Immunogenicity; E=Efficacy; RCT= Randomized Controlled Trial; Naïve = no evidence of exposure to relevant HPV type; Naïve*=in study HPV-001, subjects had no evidence of exposure to oncogenic HPV types and had normal Pap test at baseline
Non-naïve = evidence of exposure to relevant HPV type
* Double-blind, randomized, placebo-controlled studies
† Ongoing

Phase I and Phase IIa Studies

Phase I/IIa clinical studies included HPV-002, HPV-003, HPV-004 and HPV-005. GSK conducted these clinical studies from 1999-2001, and the clinical study reports and several annex reports with longer-term immune responses were submitted to the BLA as well (out to 2005). These studies assessed safety and immune response endpoints. The Phase I/IIa studies suggested an acceptable safety profile for further clinical development of the candidate VLP vaccine adjuvanted with AS04, as well as evidence of an enhanced humoral antibody response as compared to VLPs which were unadjuvanted or adjuvanted with aluminum hydroxide. **Please see attachment #2 for a brief summary of these trials.**

Phase IIb studies

Phase IIb studies (HPV-001 **a**nd its long-term extension study HPV-007) were conducted between 2001 and 2007. These studies included clinical efficacy endpoints in addition to the safety and immune response endpoints. The larger phase IIb studies provided evidence of vaccine effectiveness in prevention of incident infection with HPV 16 and/or HPV 18 in women 15-25 years of age who were initially HPV-16/18 seronegative (by ELISA) and HPV-16/18 DNA negative (by PCR). (Adolescent and young adult women that were included for the evaluation of the primary objective were seronegative for HPV-16 or HPV-18 at month 0 and were DNA negative for high risk HPV types.) Other efficacy endpoints included prevention of persistent infection with the relevant vaccine HPV type (6 month definition), prevention of abnormal cytology associated with the relevant vaccine HPV type for which the subject was naïve at baseline, and prevention of incident infection with non-vaccine HPV types which were phylogenetically related to the one of the vaccine HPV types.

The applicant's clinical development program focused on a three-dose regimen at months 0, 1, and 6. **Please see attachment #3 for a brief summary of the phase IIb clinical studies.**

Phase III Studies

HPV-008: One randomized, double-blinded, controlled phase III study evaluated the clinical efficacy, immunogenicity, and safety of Cervarix™. This study evaluated the clinical endpoints of CIN 2+ due to HPV 16 and/or 18, as well as efficacy in prevention of oncogenic HPV types not contained in the vaccine. In addition to analysis of the primary endpoint of efficacy in the primary analysis population (According to Protocol population for efficacy), other analyses of the secondary efficacy endpoints were conducted in different populations. These analyses and analysis populations are included in this document.

Efficacy of Cervarix™ in Prevention of CIN 2+ associated with HPV 16 and/or HPV 18: GSK submitted the final efficacy analysis with the re-submission of this BLA. The time of follow-up for subjects was approximately 2.9 years for the According To Protocol cohort and 3.3 years for the Total Vaccinated Cohort-1.

Study dates: The first subject was enrolled in the study on 5/6/04, the last subject was enrolled on 6/27/05, and the last subject completed her vaccination course on 6/4/06. The final event-driven analysis includes data collected up to the data lock point (DLP) of 8/31/08.

Study Sites: This study was conducted by 52 investigators in 12 countries at 57 centers (Australia, Colombia, Czech Republic, France, Germany, Honduras, Korea, Norway, Panama, Spain, Sweden and Taiwan).

Number of subjects: Of the 18,729 subjects enrolled in the study, 64 subjects were not vaccinated. An additional 21 subjects were excluded from analysis from one site at which there study integrity issues.

Within the 18665 subjects vaccinated, 21 subjects from center ---(b)(4)---- were excluded from all analyses because of potential study conduct and data integrity issues identified at this center. As a result, a total of 18644 subjects were vaccinated and included in the analyses (i.e. Total Vaccinated cohort), of whom 9319 subjects received the HPV vaccine (HPV group) and 9325 subjects received the hepatitis A vaccine (HAV group). The distribution of subjects by geographic region and country are presented below.

Table 3 - Study HPV-008: Number (%) of subjects by Geographic region and country

Region		HPV	HAV	Total/%
Asia-Pacific	**TOTAL**	**3175**	**3177**	**6352/34.1%**
By Country				
	Australia	275	273	548/2.9%
	Philippines	1232	1235	2467/13.2%
	Taiwan	743	742	1485/8.0%
	Thailand	925	927	1852/9.9%
Europe	**TOTAL**	**3224**	**3224**	**6448/34.6%**
By Country				
	Belgium	85	88	173/0.9%
	Finland	2409	2399	4808/25.8%
	Germany	387	385	772/4.1%
	Italy	18	19	37/0.2%
	Spain	191	196	387/2.1%
	United Kingdom	134	137	271/1.5%
Latin America	**TOTAL**	**1388**	**1386**	**2774/14.9%**
By Country				
	Brazil	903	900	1803/9.7%
	Mexico	485	486	971/5.2%
North America	**TOTAL**	**1532**	**1538**	**3070/16.5%**
By Country				
	Canada	253	253	506/2.7%
	United States	1279	1285	2564/13.8%
TOTAL Vaccinated Cohort		**9319**	**9325**	**18644/100%**

Adapted from STN 125259.48, CSR 008, Supplement 4, p. 10076-10079

Primary efficacy 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 Virological efficacy endpoints:

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

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

- Histopathologically-confirmed CIN1+ associated with the following oncogenic HPV types (or combination of types): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (by PCR) detected within the lesional component of the cervical tissue specimen.

Secondary 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, 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: N = ≥4000, at least 1000 per region).
- 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 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, N = ≥4000, at least 1000 per region).
- Occurrence of SAEs throughout the entire study period (Month 0 to Month 48) 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 disease (e.g. diabetes mellitus, autoimmune diseases) throughout the entire study (Month 0 to 48) in all subjects and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or 18 serostatus (by ELISA).
- Occurrence of medically significant conditions throughout entire study period (Month 0 to Month 48) and stratified by initial (Month 0) HPV-16/18 DNA status (by PCR) and according to HPV-16 or18 serostatus (by ELISA). Medically significant conditions are defined as: adverse events 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 Month 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).

Secondary Immunogenicity endpoints:

- HPV-16 and HPV-18 ELISA titers and seroconversion rates at Month 6, 7, 12, 24, 36, and 48 (in the immunogenicity subset). These analyses were stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus.
- HPV-16 and HPV-18 ELISA titres and seroconversion assessed in vaccine recipients with breakthrough HPV-16 and/or HPV-18 infections and HPV-16 and/or HPV-18 associated neoplasias, compared with selected non-cases (vaccine recipients without persistent infection or neoplasia matched for age, ethnicity and clinic site). These analyses are restricted to subjects who are seronegative for the corresponding HPV type prior to vaccination.

Analysis Populations: Different populations were used in efficacy, safety and immunogenicity analyses. The efficacy populations are presented in Table 4 below. The vast majority of subjects in study 008 were sexually active at the time of enrollment. The primary analysis was conducted in the According to Protocol population. Subjects in this cohort had a normal or low-grade cytology, were seronegative for the relevant HPV type at baseline, were PCR negative for the relevant HPV type through Month 6, and had no protocol violations. Cases were counted from 1 day after dose 3. It is important to note that **the applicant's primary analyses were specific to the HPV type.**

Cohorts similar to the ATP cohort for efficacy included the Total Vaccinated Cohort-1 (TVC-1) (protocol violators included, seronegative for the relevant HPV type at baseline, PCR negative for the relevant HPV type at baseline, cases counted after day 1) and TVC-2 (had normal cytology and otherwise same as TVC-1 cohort). (Results were generally similar to those in the ATP cohort for efficacy since subjects were seronegative and PCR negative for the relevant HPV type, although cases were counted after dose 1).

The **Total Vaccinated cohort (TVC)** was in essence an 'Intent-to-Treat' population, and included all subjects regardless of baseline status, and cases were counted 1 day after dose 1.

In order to mimic those young females who have not yet had sexual experience, a subset of subjects who were seronegative for both HPV 16 and 18 at baseline, had a normal cytology at baseline, were naïve for all **14** tested oncogenic HPV types by PCR at baseline, did not have protocol violations, received all 3 doses, and were naïve for the relevant HPV type through Month 6 were considered. This cohort was the **ATP-naïve population**, and cases were counted 1 day after dose 3. A similar cohort, the **TVC naïve population,** included a subset of subjects who may have been protocol violators, had a normal cytology at baseline, were seronegative for HPV 16 and 18 at baseline, were PCR negative for any oncogenic HPV type at baseline, with cases counted 1 day after dose 1. Efficacy results were reviewed for these different cohorts and will be specified in this review so as to present the expected impact on generally naïve subjects as well as subjects who have been infected with one or more vaccine (or non-vaccine) HPV type.

Table 4 - Study HPV-008: Efficacy Populations [CBER Generated]

Population	Protocol deviations	Pap Test Baseline	Serostatus D0	PCR status	Doses/cases counted when
ATP Cohort	No	Normal or low-grade(a)	Neg. relevant HPV	Neg. through M6 for relevant HPV type	3 doses/1 day after dose 3
TVC-1	Yes	Normal or low-grade (a)	Neg, relevant HPV	Neg. for relevant HPV type D0	1 dose/1 days after dose 1
TVC-2	Yes	Normal	Neg, relevant HPV	Neg. for relevant HPV type D0	1 dose/1 days after dose 1
TVC	Yes	All	All	All	1 dose/1 day after dose 1
ATP naive	No	Normal (b)	Neg. for HPV 16 and 18	Neg. through M6 for relevant HPV type Neg. baseline all oncogenic HPV types M0	3 dose/1 day after dose 3
TVC naive	Yes	Normal (b)	Neg. for HPV 16 and 18	Neg. for all oncogenic HPV types M0	1 dose/1 day after dose 1

(a) normal or low-grade cytology = negative or ASC-US or LSIL
(b) Normal cytology=negative or ASC-US HCII negative

In the ATP cohort for efficacy, baseline characteristics were considered for HPV 16 and HPV 18 when analyzing the results for the specific vaccine HPV type. Therefore, although there are 8093 Cervarix™ recipients and 8069 Havrix recipients in this cohort, when HPV 16 endpoints are analyzed, only those seronegative and PCR negative for HPV 16 through Month 6 are considered. Likewise, when HPV 18 endpoints are analyzed, only those seronegative and PCR negative for HPV 18 through Month 6 are considered. That explains the different number of subjects considered for specific analyses presented.

Table 5 - HPV-008: Number of subjects in each efficacy analysis population*

	Total	HPV	HAV
Total Enrolled Cohort	18729		
Total Vaccinated Cohort (TVC)	18644	9319	9325
TVC-1	18525	9258	9267

ATP cohort for efficacy	16162	8093	8069
TVC-2	17129	8544	8585
TVC naïve	10885	5449	5436
ATP naive	9258	4678	4580

*In type specific analyses, the numbers of subjects analyzed for that specific HPV type depends on the baseline status for the specific HPV type, and numbers of subjects are varied depending on the baseline status

Safety Populations:

- The **safety diary card subset** included 6371 subjects who completed diary cards. These included 3184 subjects in the vaccine group and 3187 subjects in the control group. There were 2198 subjects from Asia Pacific area, 1194 from Europe, 1471 from Latin America, and 1508 from North America in the safety subset.
- The **Total Vaccinated cohort for safety** included all subjects who received at least one dose of vaccine or active control.

Immunogenicity populations:

- The **ATP cohort for immunogenicity** included 1933 subjects (1035 subjects in the HPV group and 898 subjects in the HAV group). In order to evaluate the immune response to the vaccine, factors possibly influencing the immune response were to be considered. Therefore, subjects who acquired either HPV-16 or HPV-18 infection during the trial (including baseline), which may influence HPV antibody levels, were excluded from the ATP cohort for immunogenicity. Due to the efficacy of the HPV vaccine, more subjects developed HPV-16/18 infections in the HAV group than in the HPV group (2117 versus 1119 subjects) and thus were eliminated from the ATP cohort for immunogenicity. This again makes assessment of immune response in the TVC for immunogenicity important.
- The **Total Vaccinated cohort** for analysis of immunogenicity includes subjects who were eliminated from the ATP cohort for immunogenicity.

Results

Withdrawals due to Adverse Events: The proportions of subjects who withdrew from the Total vaccinated Cohort were comparable in each treatment group (9.3% HPV group and 9.2% in the control group).

Compliance with completion of the three-dose vaccination schedule was high and comparable in both groups: 91.6% in the HPV group and 91.9% in the HAV group.

Subject characteristics in Efficacy cohorts:

The demographic profile of both groups of subjects was comparable with respect to mean age, regional distribution, ethnic distribution, mean height and weight. The mean age was 19.9 years and the population was predominantly of Caucasian or East/South East Asian origin (57.4% and 21.9%, respectively).

In the ATP cohort for efficacy, 91% of subjects overall had a normal cytology. Overall, 14.4% of subjects with a 'normal' cytology were infected with one of the HR-HPV types tested. When one considers subjects with a 'low-grade cytology', approximately 28% are infected with one of the vaccine HPV types, and app. 70% are infected with any of the tested HR-HPV types. The proportions of subjects in the TVC with normal or low-grade cytology and infected with any HR-HPV types are similar to those in the ATP cohort for efficacy. A very low proportion of subjects had a high grade cytological abnormality (0.5% overall). App. 91% of subjects with high grade cytological abnormalities were infected with a HR-HPV type, and app. 57% were infected with one or both of the vaccine HPV types.

Histopatholgical Case Ascertainment
All specimens were evaluated by two panels of histopathologists. The specimens were examined by a routine panel of histopathologists, who provided the histopathological diagnosis used for clinical management of the subject. The routine panel consisted of two designated, expert pathologists who independently evaluated the study specimens. In case of disagreement in diagnosis between the two pathologists, a third expert panel member examined the specimen and a consensus diagnosis was reached. The consensus diagnoses were placed in the results reporting system and made available electronically at each site within a designated timeframe of receipt at Quest.

Following the review by the routine panel, tissue samples and slides with a diagnosis of CIN1, VIN1, VaIN1 or higher were sent to a second panel of histopathologists (the study panel) for the purpose of endpoint determination. This second histopathological review process was performed in a blinded way, without knowledge of the diagnosis previously made by the routine panel. The study panel consisted of three expert gynecological pathologists under the supervision of a fourth pathologist. This fourth pathologist coordinated the independent and blind review process, and ensured that agreement on the grade level and location of the lesion in the tissue was obtained between at least two members of the study panel. When multiple areas of abnormality were present in a single tissue specimen, the most severe area constituted the study endpoint.

The final analysis was triggered with confirmation of at least 36 cases of CIN2+ associated with HPV-16/18 (by PCR) (including at least 15 cases of CIN2+ associated with HPV-18 infection) post dose 3 in subjects who were HPV DNA negative at Month 0 and 6 and seronegative at baseline. At the time of the final analysis there were 60 cases of the primary endpoint in the ATP cohort for efficacy (48 cases associated with HPV-16, 17 cases associated with HPV-18 and 5 cases associated with both HPV-16 and HPV-18) in subjects who were HPV DNA negative at Month 0 and 6, and seronegative at Month 0, for the corresponding type found in the lesion. Case numbers were assigned by the external statistician. Case numbers 1 to 23 were already identified at interim analysis in the TVC-1 cohort, whereas case numbers above 23 were additional cases identified at final analysis.

EFFICACY RESULTS HPV-008
Efficacy in *Prevention of CIN 2+ related to HPV 16 and/or 18* in females 15-25 years of age *naïve for the relevant vaccine HPV type*: In the protocol-specified primary endpoint analysis the objective was met with vaccine efficacy against CIN2+ associated with HPV-16/18 of 92.9% [79.9, 98.3] (4 cases in the HPV group versus 56 cases in the HAV group). Statistically significant vaccine efficacy was observed inidivdually for CIN2+ associated with HPV-16 (VE=95.7% [82.9, 99.6]) and HPV-18 (VE=86.7% [39.7, 98.7]). Please note that the lower and upper bound of the 96.1% CI were used in analyses (adjustment taken in view of interim analysis). These analyses were conducted in women naïve (seronegative at baseline and PCR negative through Month 6) for the relevant vaccine HPV type, with a normal or low-grade cytology, and with cases counted 1 day after receipt of dose 3.

Table 6 -HPV-008: Incidence rates and vaccine efficacy against *CIN2+* associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	7344	4	17689.6	0.02 [0.01, 0.06]	92.9% [79.9, 98.3%]
	HAV	7312	56	17663.32	0.32 [0.24, 0.42]	-
HPV 16	**HPV**	6303	2	15193.63	0.01 [0.00, 0.05]	85.7% [82.9, 99.6%]
	HAV	6165	46	14911.49	0.31 [0.22, 0.42]	-

HPV 18	**HPV**	6794	2	16377.95	0.01 [0.00, 0.05]	86.7% [39.7, 98.7%]
	HAV	6746	15	16310.82	0.09 [0.05, 0.16]	-

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type
For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Table 31, p. 237

An additional endpoint of interest was the vaccine efficacy in prevention of HPV 16 and/or 18 related CIN3+ in the ATP cohort for efficacy, and the point estimate for this endpoint [80%; 0.3, 98.1%] reached statistical significance.

When cases are counted after day 1 in subjects who were naïve at baseline for the relevant vaccine HPV type and a normal or low-grade cytology (TVC-1 cohort), high efficacy [94.5%; 86.2, 98.4%] for the combined HPV 16 and/or 18 CIN2+ cases was also demonstrated. In this population, there were 96 cases of CIN2+ associated with HPV-16/18 in subjects who were HPV DNA negative and seronegative for the corresponding type at baseline. (The point estimates for efficacy analyses in this cohort reached statistical significance for HPV 16 and 18 individually). In this same TVC-1 cohort, where cases were counted after day 1, vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 90.9% [60.8, 99.1%].

12- month and 6-month persistent infections for the relevant HPV types were assessed as secondary endpoints. There is no accepted definition of HPV persistence which is clinically relevant, although it has been reported that persistent infection over 1 year (and especially 2 years) may predict higher risk of progression to pre-cancer or cancer (at least in women 30 years of age or younger). [6,7]

Other histopathological and virological endpoints with HPV-16/18 in subjects naïve for the relevant vaccine HPV type

Table 7 - HPV-008: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline using conditional exact method (ATP cohort for efficacy)

				VE
Endpoint	**Group**	**N**	**n**	**% [96.1% CI]**
CIN 1+ associated with HPV 16 and/or HPV 18	HPV	7344	8	91.7% [82.4, 96.7%]
	HAV	7312	96	
Incident infection HPV 16 and/or HPV 18	HPV	7346	263	76.7% [73.2, 79.9%]
	HAV	7320	1074	
Persistent infection (6-month) HPV 16 and/or HPV 18	HPV	7177	32	93.8% [91.0, 95.9%]
	HAV	7122	497	
Persistent infection (12-month) HPV 16 and/or HPV 18	HPV	7035	21	91.2% [85.9, 94.8%]
	HAV	6984	233	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type; For combined types: Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for at least one HPV type (subjects were in the analysis of at least one single type); n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period starts at day after Dose 3; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits

[6] Schiffman M et al. Human papillomavirus and cervcal cancer. The Lancet (2007); 370: 890-907

[7] Rodriguez C et al. JNCI 2008;100:513-517.

The point estimates for HPV 16 and HPV 18 individually are near to those in the combined analyses provided above and reach statistical significance. There are in general fewer cases related to HPV 18 as compared to HPV 16 in all analyses.

Overall CIN2+ associated with HPV-16/18, irrespective of baseline HPV DNA and Serostatus: The vaccine efficacy in the Total Vaccinated Cohort against CIN2+ associated with HPV-16/18 irrespective of baseline HPV DNA and serostatus was 52.8% [37.5, 64.7] with 82 cases in the HPV group and 174 cases in the HAV group. The point estmates of vaccine efficacy in prevention of CIN2+ associated with HPV-16 or HPV-18 irrespective of baseline HPV DNA status also reached statistical significance. It is important to keep in mind that this population includes subjects who were naïve and non-naïve for the relevant vaccine HPV type, and the results in the naïve population may help drive these results. (In comparison, the point estimate for Gardasil for the combined HPV 16/18 related CIN2+ in a similar population was 51.8% [95% CI: 41.1, 60.7%])**.**

Table 8 - HPV-008: Incidence rates and vaccine efficacy against *CIN2+ associated with HPV-16 and/or HPV-18* (by PCR) in all subjects, *irrespective of their baseline HPV DNA and serostatus,* using conditional exact method (Total Vaccinated cohort)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	8667	82	24825.41	0.33 [0.26, 0.41]	52.8% [37.5, 64.7%]
	HAV	8682	174	24846.52	0.70 [0.60, 0.82]	-
HPV 16	**HPV**	8667	75	24837.48	0.30 [0.23, 0.38]	50.6% [33.5, 63.6%]
	HAV	8682	152	24878.73	0.61 [0.51, 0.72]	-
HPV 18	**HPV**	8667	8	24958.28	0.03 [0.01, 0.06]	75.7% [44.4, 90.8%]
	HAV	8682	33	25027.68	0.13 [0.09, 0.19]	-

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
All subjects included, irrespective of their baseline HPV DNA status; n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Supplement 192 p. 10391

Efficacy in *Prevention of CIN 2+ associated with ANY HPV type in Total Vaccinated Cohort:* The point estimate of efficacy for prevention of CIN 2+ associated with ANY HPV type is 30.4% [16.4, 42.1%] in the Total Vaccinated Cohort. This analysis includes all subjects (both naïve and non-naïve) and with varying Pap tests. CBER notes that the overall point estimate of efficacy in prevention against CIN2+ associated with any HPV type is higher in study HPV-008 for Cervarix^{tTM} as compared to results in a similar population in the Gardasil BLA (18.4% [95% CI: 7.0, 27.7%]) for a similar population. However, some differences noted between the two studies included the fact that there was a lower proportion of subjects in the Cervarix^{TM} study with a high grade Pap test at baseline (0.5% with HSIL) as compared to the proportion of subjects in the combined Gardasil trials (1.0%). In addition, cases were counted after day 1 in the Cervarix^{TM} study as compared to day 31 in the Gardasil studies. Further, the pathologists and algorithm differed between the GSK study as compared to the Merck study. The times of follow-up were similar (39 months for Cervarix^{TM} and approximately 42 months for Gardasil) in both trials.

Table 9 - HPV-008: Incidence rates and vaccine efficacy against CIN2+, irrespective of HPV DNA results, irrespective of subjects HPV DNA and serostatus at baseline using conditional exact method (Total Vaccinated cohort)

				Person-year rate	VE
Group	**N**	**n**	**T (year)**	**n/T (per 100)**	**% [96.1% CI]**
HPV	8667	224	24627.29	0.91 [0.79, 1.04]	30.4% [16.4, 42.1%]
HAV	8682	322	24658.87	1.31 [1.16.1.46]	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer

All subjects included, irrespective of their baseline HPV DNA status; n=number of subjects reporting at least one event in each group
T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group
Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.48, CSR 008, Table 87, p. 332

Positive point estimates of efficacy were also noted in the Total Vaccinated Cohort for CIN 3+ related to ANY HPV type (VE=33.4% [9.1, 51.5%]) and for CIN 1+ related to ANY HPV type (VE=21.7% [10.7, 31.4%]).

In an exploratory analysis, a reduction in rates of local cervical therapy was noted in the Total Vaccinated Cohort (VE=24.7% [7.4, 38.9%]).

Efficacy in prevention of *CIN2+ associated with ANY HPV type who had normal cytology and* were *not infected with any tested HPV at baseline:* There was a 70% reduction in CIN 2+ related to any HPV type in this cohort of uninfected subjects (see Table 10 below). This point estimate of efficacy for the 'naïve' population was higher than the one reported for Gardasil (VE = 42.7% [95% CI: 23.7, 57.3%]. This reviewer notes that the 'naïve' populations analyzed in each manufacturer's study were different. Subjects participating in the GSK study were tested for 14 oncogenic HPV types at baseline (as well as 11 non-oncogenic HPV types as well) as compared to 12 oncogenic and 2 non-oncogenic HPV types tested in the Gardasil BLA. In addition, ascertainment of cases was by a somewhat different algorithm and conducted by a different panel of pathologists. Also, cases were counted after day 1 for the GSK study from 1 day after month 1 in the Gardasil studies. The issue of whether there is reduction of genital dysplasias related to non-vaccine HPV types as well as vaccine HPV types in this "naïve" population is a point to consider.

Table 10 - HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with ANY HPV DNA results, in HPV naïve subjects at baseline, using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	VE
Group	**N**	**n**	**T (yesr)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV	5449	33	15771.51	0.21 [0.14, 0.30]	70.2% [54.7, 80.9%]
HAV	5436	110	15690.39	0.70 [0.57, 0.85]	-

CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer; N=number of subjects included in each group
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0
n=number of subjects reporting at least one event in each group; T(years)=sum of follow-up period (censored at the first occurrence of an event) expressed in years in each group; Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event; VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.48, CSR 008, Supplement 290, p. 10485

Point estimates of efficacy for prevention of CIN3+ related to any HPV type (VE=87% [54.9, 97.7%] amd CIN1+ related to any HPV type (VE=50.1% [35.9, 61.4%] were also reported in the TVC-naïve cohort. In an exploratory analysis, a reduction in local cervical therapy in this naïve subset was also noted (68.8% [50.0, 81.2%]).

Efficacy in *prevention of CIN2+ associated with HPV 16 and/or 18 in subjects non-naïve (seropositive and/or PCR positive) for the relevant vaccine HPV type*: Results for vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 in subjects who were HPV DNA positive at baseline indicated a lack of therapeutic effect and point estimates were not statistically significant. In subjects who were HPV DNA positive and/or seropositive at baseline the vaccine efficacy against CIN2+ with HPV-16/18 was 1.5% [-43.3, 32.3]), in TVC-1.

Table 11 - HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 (by PCR) in subjects who were HPV DNA positive *and/or* seropositive subjects at baseline, using conditional exact method (subjectst with low-grade cytology)

					Person-year rate	VE
Event Type	**Group**	**N**	**n**	**T (yesr)**	**(n/T) per 100 [95% CI]**	**% [96.1% CI]**
HPV 16/18	**HPV**	2189	65	6134.87	1.06 [0.81, 1.37]	1.5% [-45.3, 32.3%]
	HAV	2211	67	6230.09	1.08 [0.82, 1.38]	-
HPV 16	**HPV**	1619	60	4512.35	1.33 [1.00, 1.73]	2.6% [-43.9, 34.2%]
	HAV	1623	62	4539.72	1.37 [1.03, 1.77]	-
HPV 18	**HPV**	1095	6	3097.58	0.19 [0.07, 0.44]	-0.1% [-299.8, 75.0%]
	HAV	1088	6	3099.59	0.19 [0.07, 0.44]	-

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
For single type: Subjects DNA positive or seropositive for the corresponding HPV type at Month 0
For combined types: Subjects DNA positive or seropositive for either HPV-16 or HPV-18 at Month 0
n=number of subjects reporting at least one event in each group; T(years)=sum of follow-up period
(censored at the first occurrence of an event) expressed in years in each group; Follow-up period started at day after Dose 1
n/T=Incidence rate of subjects reporting at least one event; VE(%)=Vaccine Efficacy (conditional exact method)
LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Supplement 186, p. 10386

When considering subjects who were HPV DNA positive at baseline, there was an apparent imbalance in number of CIN2+ lesions associated with HPV-16/18 in subjects who were HPV DNA positive and seropositive at baseline in subjects with a normal or low-grade cytology [TVC-1] (43 cases versus 31 cases in HPV and HAV groups, respectively), although this imbalance was slightly less than observed at the interim analysis (33 cases versus 18 cases in HPV and HAV groups, respectively). This may indicate greater accrual of cases in the HAV group than in the HPV group between the interim and final analyses. There was little difference observed for CIN1+ associated with HPV-16/18 in the same subset of subjects (44 cases versus 40 cases in HPV and HAV groups, respectively). The analysis of HPV DNA positive subjects was conducted in a small subset of subjects (N=1184) and none of the differences observed between groups in the above analysis were statistically significant.

Table 12 - HPV-008: Overview of vaccine efficacy against histological lesions associated with HPV-16/18 in HPV DNA positive subjects for relevant vaccine HPV type in TVC-1 (with normal or low-grade cytology)

	HPV		**HAV**		**VE**
Event Type	**N**	**n**	**N**	**n**	**% [96.1% CI]**
HPV DNA positive and seronegative subjects at baseline					
CIN2+	303	18	285	27	37.8% [-20.9, 69.9%]
CIN1+	303	27	285	36	30.5% [-20.9, 60.5%]
HPV DNA positive and seropositive subjects at baseline					
CIN2+	315	43	290	31	-32.5% [-123.1, 20.4%]
CIN1+	315	44	290	40	-3.0% [-66.0, 35.9%]
HPV DNA positive at baseline, regardless of initial serostatus					
CIN2+	617	62	567	58	0.5% [-47.7, 32.9%]
CIN1+	617	72	567	76	13.0% [-23.8, 38.9%]

CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group; n=number of subjects reporting at least one event in each group
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Table 100, p. 358

The sponsor notes that the randomization scheme used in this study did not take into account the HPV DNA status at baseline. It was already noticed at the interim analysis that the distribution of subjects with low-grade cytology at baseline was not exactly balanced between groups. This may help explain the numerical imbalance in cases of CIN2+ in the subgroup of subjects that had abnormal cytology and were HPV DNA positive and seropositive at baseline. In review of the the subjects in this subgroup who developed CIN2+, a slightly higher proportion of Cervarix™ recipients (71.9%) had an abnormal cytology at baseline as compared to 68.8% in the Havrix

group. The majority of cases in both groups developed CIN2+ lesions within 7 months of entry into the study (68.4% HPV, 75.6% HAV). Other factors such as coinfections with other HPV types are not known, nor can the exact duration of infection be determined (since these women were PCR positive at baseline).

From all study panel-ascertained CIN2+cases, CBER assessed the breakdown by treatment group in subjects seropositive and PCR positive for the relevant HPV types regardless of baseline cytology (i.e., included all such cases). The numerical imbalance was seen in this comparison as well. It appears that 14 additional cases were added to each group when including subjects with higher grade baseline cytological abnormalities as compared to when subjects with low-grade or normal cytology are considered.

Table 13 - HPV-008: CIN 2+ cases: Number of cases Seropositive and PCR positive for relevant vaccine HPV type, cases post day 1 [CBER generated]

Group	HPV N=9319	HAV N=9325
Number of subjects with CIN2+ related to relevant HPV type for which they were seropositive and PCR positive at baseline (any cytology)	57	45

HPV group:
Abnormal Pap = 41/57 (71.9%); 13 with HSIL, ASC-H; 13 with LSIL, 15 with ASC-US+
Time of diagnosis: 12 @M0-1; 27@M6-7
39/57 within 7 months=68.4%

HAV group:
Abnormal Pap=31/45 (68.8%); 12 with HSIL, ASC-H; 10 with LSIL; 9 with ASC-US+
Time of diagnosis: 14@M0-1; 30@M6-7
34/45 within 7 months = 75.6%

The sponsor also notes that when considering the overall number of subjects with abnormal cytology at entry progressing to CIN2+ (a total of 1484 subjects had abnormal cytology at baseline), there were 103 subjects in HPV group (13.6%) and 101 in the HAV group (13.9%) with progression to CIN2+. Therefore, administration of vaccine subjects with abnormal cytology did not enhance the risk of developing CIN2+.

CIN2+ related to non-vaccine oncogenic HPV types
Considering the multiple oncogenic HPV types with which a woman may be infected and assessing the impact of Cervarix™ in reducing CIN2+ related to these non-vaccine HPV types have proven to be a complicated process.

GSK has presented several secondary and exploratory analyses of reduction of CIN2+ associated with specific non-vaccine HPV types in the ATP cohort for efficacy, in the TVC-1 cohort, and the TVC-naïve cohort, along with reduction of persistent infection in the ATP and TVC-1 cohorts. The only non-vaccine HPV type for which all point estimates of efficacy reach statistical significance is HPV-31. The CBER statistician has noted that no multiplicity adjustments were made in calculating the efficacy when considering the 14 different HPV types, thereby introducing Type I error. Statistical significance was maintained for HPV-31 only after further alpha adjustment. Point estimates of efficacy for CIN2+, 6-month and 12-month persistent infection in the ATP cohort for efficacy are shown for HPV types 31 and 45 in the table below. HPV-31 is phylogenetically related to HPV-16 and HPV-45 is phylogenetically related to HPV-18.

Table 14 - HPV-008: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-31 and HPV 45 (by PCR) in HPV DNA negative and seronegative subjects at baseline with normal or low-grade cytology using conditional exact method (ATP cohort for efficacy) [cases counted after Month 6]

		VE
Endpoint	n*	% [96.1% CI]
CIN 2+ associated with HPV 31	2/25	92.0% (66.0, 99.2%)
Persistent infection (6-month) with HPV 31	46/215	78.7% (70.2, 85.2%)
Persistent infection (12-month) HPV 31	21/102	79.4% (66.1, 88.1%)
CIN 2+ associated with HPV 45	0/5	100% (-67.8, 100%)
Persistent infection (6-month) with HPV 45	23/94	75.7% (60.4, 85.7%)
Persistent infection (12-month) HPV 45	10/27	63.0% (18.4, 84.7%)

*n=number of subjects reporting at least one event in each group (HPV group/HAV group)

Table 15 - HPV-008: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-31 and HPV 45 (by PCR) in HPV DNA negative and seronegative in subjects at baseline with normal or low-grade cytology using conditional exact method (TVC-1) [cases counted after Day 1]

		VE
Endpoint	**n***	**% [96.1% CI]**
CIN 2+ associated with HPV 31	11/34	67.4% (32.0, 85.7%)
Persistent infection (6-month) with HPV 31	94/283	66.9% (57.6, 74.4%)
Persistent infection (12-month) HPV 31	52/138	62.3% (46.9, 73.6%)
CIN 2+ associated with HPV 45	0/5	100% (-20.2, 100%)
Persistent infection (6-month) with HPV 45	35/123	71.6% (57.6, 81.5%)
Persistent infection (12-month) HPV 45	19/43	55.8% (20.4, 76.4%)

*n=number of subjects reporting at least one event in each group (HPV group/HAV group)

CBER further assessed efficacy for non-vaccine HPV types in the TVC-naïve population since these women appear to be naïve for all 14 oncogenic HPV types tested at baseline (seronegative for HPV 16/18 at baseline, PCR negative at baseline for all 14 oncogenic HPV types, and cytology negative). It is acknowledged that serostatus for the non-vaccine HPV types were not tested, although baseline serostatus for HPV 16 and/or 18 does not seem to impact on results in other efficacy analyses. The analyses as calculated by GSK are included in Table 16 below.

Table 16 - HPV-008: Incidence rates and vaccine efficacy against CIN2+ associated with oncogenic HPV types (by PCR) in HPV naïve subjects at baseline using conditional exact method (Total cohort of HPV naïve women)

				Person-year rate	**VE**
Event Type	**Group**	**N**	**n**	**(n/T) per 100 [96.1% CI]**	**% [96.1% CI]**
HPV-16	**HPV**	5449	1	0.01 [0.00, 0.04]	98.2% [89.1, 100%]
	HAV	5436	56	0.36 [0.26, 0.47]	
HPV-18	**HPV**	5449	0	0.00 [0.00, 0.02]	100% [61.3, 100%]
	HAV	5436	12	0.08 [0.04, 0.14]	
HPV-31	**HPV**	5449	0	0.00 [0.00, 0.02]	100% [78.3, 100%]
	HAV	5436	20	0.13 [0.08, 0.20]	
HPV-33	**HPV**	5449	5	0.03 [0.01, 0.08]	72.3% [19.1, 92.5%]
	HAV	5436	18	0.11 [0/07, 0.18]	
HPV-35	**HPV**	5449	1	0.01 [0.00, 0.04]	75.1% [-176.3, 99.6%]
	HAV	5436	4	0.03 [0.01, 0.07]	
HPV-39	**HPV**	5449	3	0.02 [0.00, 0.06]	66.8% [-41.4, 94.8%]
	HAV	5436	9	0.06 [0.02, 0.11]	
HPV-45	**HPV**	5449	0	0.00 [0.00, 0.02]	100% [-19.5, 100%]
	HAV	5436	5	0.03 [0.01, 0.08]	
HPV-51	**HPV**	5449	2	0.01 [0.00, 0.05]	88.3% [47.9, 98.9%]
	HAV	5436	17	0.11 [0.06, 0.18]	

HPV-52	**HPV**	5449	7	0.04 [0.02, 0.09]	36.5% [-67.1, 100%]
	HAV	5436	11	0.07 [0.03, 0.13]	
HPV-56	**HPV**	5449	0	0.00 [0.00, 0.02]	100% [-67.1, 100%]
	HAV	5436	4	0.03 [0.01, 0.07]	
HPV-58	**HPV**	5449	3	0.02 [0.00, 0.06]	72.8% [-8.9, 95.6%]
	HAV	5436	11	0.07 [0.03, 0.13]	
HPV-59	**HPV**	5449	0	0.00 [0.00, 0.02]	100% [-514.5, 100%]
	HAV	5436	2	0.01 [0.00, 0.05]	
HPV-66	**HPV**	5449	1	0.01 [0.00, 0.04]	83.4% [-48.0, 99.7%]
	HAV	5436	6	0.04 [0.01, 0.09]	
HPV-68	**HPV**	5449	2	0.01 [0.00, 0.05]	71.5% [-60.3, 97.5%]
	HAV	5436	7	0.04 [0.02, 0.09]	

N=number of subjects included in each group; CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
Subjects DNA negative for all high risk HPV types, seronegative for HPV-16 and HPV-18 and negative cytology, at Month 0; n=number of subjects reporting at least one event in each group;
Follow-up period started at day after Dose 1; n/T=Incidence rate of subjects reporting at least one event
VE(%)=Vaccine Efficacy (conditional exact method); LL,UL=96.1% Lower and Upper confidence limits
Source: STN 125259.0048. CSR 008, Supplement 273, p. 10469

From Table 16 above, it is noted that point estimates of efficacy reach statistical significance in prevention of CIN 2+ associated with HPV 16, 18, 31, 33, and 51 in the TVC-naïve cohort. The point estimates for efficacy in prevention of persistent infection (6-month) in this totally naïve population were statistically significant for HPV 16, 18, 31, 33, 45 and 51 as well. The alpha adjustment included was related to the interim analysis, not for tests of multiple HPV types. The evaluation of histopathologically confirmed CIN2+ associated with the 14 oncogenic HPV type was not evaluated for multiplicity. Vaccine efficacy associated with HPV-31 may be the only non-vaccine HPV type which showed statistically significant results.

In order to better assess the impact of the vaccine on prevention CIN2+ associated with specific vaccine and non-vaccine HPV types, CBER reviewed the study pathology panel-ascertained cases of CIN2+ in women in the TVC-naïve population from the datasets and tables of these cases provided by GSK. The tables below include the CIN2+ cases related to the vaccine and non-vaccine HPV types in this nive population.

Table 17 - HPV-008: CIN 2+ Cases associated with HPV 16 and/or 18 in subjects who were naïve for all 14 oncogenic HPV types tested, Seronegative for HPV 16/18, Pap negative at baseline (TVC naïve) [CBER generated]

	Havrix N=5436	Cervarix™ N=5449
HPV type	Number of cases w/16/18	Number of cases w/ 16/18
16 alone	21	1
18 alone	5	0
16,18 alone	1	0
16 with other HPV types	29	0
18 with other HPV types	2	0
16, 18 with others	5	0

N=number of subjects in TVC-naïve cohort

In the TVC-naïve group in Table 17 above, the one subject identified in the Cervarix™ group who developed a CIN2+ lesion related to HPV 16 was noted to be infected with HPV 16 and 43 by Month 6 (prior to completion of vaccination series), and the lesion was diagnosed at Month 18.

The number of CIN2+ cases ascertained from the datasets were generally the same as in the GSK analyses for the TVC-naïve population. A number of lesions which occurred in the Havrix group were also associated with a vaccine HPV type. A number of cases in the Cervarix™ and Havrix groups were also associated with other non-vaccine HPV types as well. A total is also provided

to show case splits when lesions with a vaccine HPV type are excluded from the totals. The last column provides the number of cases in the HAV and HPV groups when the non-vaccine HPV type is considered alone.

Table 18 - HPV-008: CIN 2+ cases associated with specific non-vaccine HPV types in subjects naïve for all oncogenic HPV types, S- 16/18 at baseline, Pap – at baseline, cases counted post dose 1 (TVC-naïve)[CBER generated]

HPV type	HAV group N=5436				HPV group N=5449				**HAV:HPV Excluding HPV 16/18**	HAV:HPV Cases due to non-vaccine HPV type alone
	Total	Non-vaccine type alone	With others (new non-vaccine HPV types)	**With HPV 16/18**	**Total**	Non-vaccine type alone	With others (new non-vaccine HPV types)	**With HPV 16/18**		
31	**22**	6	9	**7**	**2**	0	2	**0**	**15:2**	6:0
33	**19**	9	6	**4**	**6**	3	3	**0**	**15:6**	9:3
35	**4**	1	1	**2**	**1**	1	0	**0**	**2:1**	1:1
39	**9**	1	3	**5**	**3**	2	1	**0**	**4:3**	1:2
45	**4**	0	1	**3**	**0**	0	0	**0**	**1:0**	0:0
51	**19**	3	2	**14**	**2**	2	0	**0**	**5:2**	3:2
52	**11**	1	2	**8**	**8**	6	2	**0**	**3:8**	1:6
56	**4**	0	1	**3**	**2**	0	2	**0**	**1:2**	0:0
58	**11**	2	4	**5**	**3**	2	1	**0**	**6:3**	2:2
59	**1**	0	0	**1**	**0**	0	0	**0**	**1:0**	0:0
66	**5**	1	2	**2**	**1**	0	1	**0**	**3:1**	1:0
68	**8**	1	1	**6**	**0**	0	0	**0**	**2:0**	1:0

CBER also reviewed the number of CIN2+ cases in subjects who were naïve for the relevant HPV type at baseline (not just those who were totally naïve at baseline). The total number of cases detected for each HPV type listed includes those who were naïve for all types and those who were naïve for the relevant non-vaccine HPV type (but may have been positive for other HPV types at baseline).

Table 19 - HPV-008: Cases of CIN 2+ in subjects naïve relevant for non-vaccine HPV type (includes TVC naïve subjects) [CBER generated]

Non-HPV type	**HAV:HPV Including HPV 16/18**	**HAV:HPV Excluding HPV 16/18**	**HAV:HPV Cases due to non-vaccine HPV type alone**
31	36:11	27:11	9:3
33	34:16	25:16	14:5
35	9:1	6:1	3:1
39	15:5	8:5	1:3
45	5:0	1:0	0:0
51	43:13	23:13	12:7
52	16:19	7:19	1:10
56	11:7	6:7	0:0
58	20:8	13:8	4:5
59	5:5	4:5	0:2
66	11:4	9:4	2:1
68	15:5	9:5	2:2

There may be a decrease in lesions related to HPV-31 in subjects who were naïve for all oncogenic HPV types, as well as naïve for HPV-31 specifically. CBER was also interested in the results for HPV-45, given the apparent efficacy in prevention of persistent infection with HPV-45 (6-month and 12-month) in the ATP cohort and TVC-1 cohort, and the 5:0 case split for CIN2+ lesions associated with HPV 45. The following characteristics were noted for these cases which

occurred in the HAV group: 1 subject had prior infection with HPV 16, and the lesion contained HPV 16 and 45. Three subjects developed lesions associated with HPV 16 and 45 (and these subjects were naïve for both at baseline). One subject developed a lesion with HPV 45 and 58 (and had been naïve for both).
Also noted in the all naïve group and in the group naïve for the relevant HPV type was a higher number of CIN2+ cases related to HPV-52 in the Cervarix™ group as compared to the HAV group.

For other non-vaccine HPV types in a subset of subjects who were PCR positive for the relevant non-vaccine HPV type, there was no apparent prevention of CIN2+ lesions for these subjects, expcept for perhaps HPV-45 (see text below for discussion). A total of CIN2+ cases from the datasets are provided below.

Table 20 - HPV-008: CIN 2+ cases associated with non-vaccine HPV type for which subject was PCR positive at baseline [CBER generated]

HPV type	HAV group	HPV group
31	15	19
33	12	12
35	4	4
39	6	3
45	7	0
51	16	13
52	19	18
56	7	1
58	9	12
59	1	1
66	7	5
68	3	1

GSK's exploratory analysis of efficacy for HPV-45 in subjects who were HPV-45 DNA positive at baseline is shown below.

Table 21 - HPV-008: CIN2+ cases associated with HPV 45 identified in subjects who were PCR positive for HPV 45 at baseline (GSK exploratory analysis)

		VE
Endpoint	**n***	**% [96.1% CI]**
CIN 2+ associated with HPV 45	0/7	**100% [20.7, 200%]**

*n=number of subjects reporting at least one event in each group (HPV group/HAV group)

In review of these 7 cases of HPV-45 related CIN2+ in subjects who were PCR positive for HPV-45 at baseline (which developed in HAV recipients), all 7 had HPV 45 present at baseline, and 2/7 lesions were detected at Month 1. One of the cases detected at Month 1 also had HPV 16 and 51 present at baseline. Another subject with a lesion detected at Month 1 had HPV 16 and 31 present at baseline. Another subject with a 45-related lesion at Month 12 had HPV 16, 31, 33, 51, 52, and 56 present at baseline, and another subject who developed a 45-related lesion at Month 36 was coinfected with HPV 52 at baseline, and then had persistent HPV 51 infection along with HPV 45 infection from Month 6 to Month 36. One subject was also infected with HPV 16, 31, and 66 at baseline and developed a lesion associated with HPV 16 and 45 at Month 24. One subject with HPV 45 alone in the lesions developed CIN2+ at Month 6 and one at Month 12. The duration of time of infection was not able to be determined in subjects positive at baseline.

Efficacy against VIN1+ and/or VaIN 1+
VIN 2/3 or VaIN 2/3 were not assessed as endpoints, although efficacy was assessed in prevention of VIN1+ and/or VaIN1+ associated with HPV 16/18 in subjects who were naïve for

the relevant vaccine HPV type. In the clinical study report for study HPV-008, the sponsor presents the few cases which have occurred within Study HPV-008, and although vaccine efficacy is estimated at 100% for each of the combined HPV 16 and/or 18 VIN 1+ or VaIN 1+ composite endpoints, these point estimates do not reach statistical significance. Clinically relevant endpoints include VIN 2/3 and VaIN 2/3.

The incidence rates and vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 (by PCR) in HPV DNA negative and seronegative subjects at baseline in the ATP cohort for efficacy are presented. There were 12 cases of VIN1+/VaIN1+ associated with HPV-16/18 included in this analysis. The vaccine efficacy against VIN1+/VaIN1+ associated with HPV-16/18 was statistically significant (VE=80.0% [0.3, 98.1]), with 2 cases in the HPV group versus 10 cases in the HAV group. There were 2 cases of VIN1+/VaIN1+associated with HPV-16 in the HPV group and 6 in the HAV group. There were only 4 cases of VIN1+/VaIN1+ associated with HPV-18, which were all in the HAV group.

The incidence rates and vaccine efficacy against VIN1+ or VaIN1+, irrespective of HPV DNA type detected in the lesion, in subjects who were DNA negative for all HPV types at baseline, regardless of initial serostatus, in the ATP cohort for efficacy are presented. The vaccine efficacy was statistically significant at 60.3% [11.3, 83.7]), with 10 cases in the HPV group versus 25 in the HAV group.

IMMUNOGENICITY RESULTS HPV-008

As in study HPV-001/007, IgG antibodies to HPV 16 and HPV 18 as measured by ELISA peaked after dose 3, then decreased and reached a plateau from Month 18-24 onward. GMTs remained much higher than those noted in the control group, and as compared to subjects with evidence of natural infection. In study HPV-008, immune responses were measured in the immunogenicity subset. In the ATP cohort for immunogenicity, 100% of Cervarix™ recipients were seropositive (≥8 EL.U/ml for HPV 16 and ≥7 EL.U/mL for HPV 18 when measured by ELISA) at Month 36 in the study.

Neutralizing antibodies to HPV-16 and HPV-18 were also measured in study HPV-008 in a subset of subjects. The results obtained by Peripheral Blood Neutralizing Assay (PBNA) follow a similar pattern to the IgG antibodies to HPV 16 and 18 as measured by ELISA. All evaluated subjects in the HPV group were seropositive for anti-HPV-16 and anti-HPV-18 neutralizing antibodies at Month 24 (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 through Month 24.

Immunogenicity results were previously discussed in the section with Phase IIb studies (please see attachment 3).

Additional Phase III studies were conducted to assess consistency of lots prepared by different manufacturing processes and to compare immune responses in 15-25 year old women as compared to 10-14 year old females (Study HPV-012), and to assess lot consistency between different lots by final manufacturing processes (Study HPV-016). (Please see attachment #4 for a brief summary of the lot consistency studies HPV-012 and HPV-016).

An additional study (HPV-014) was conducted to compare immune responses elicited by Cervarix™ in women 15-25 years of age as compared to women 26-55 years of age. Since the Phase III study to assess efficacy in women 26-55 years of age is ongoing (HPV-015), and the BLA does not provide data which is considered supportive of approval in this older age population, the immunogenicity results for women > 25 years of age are not included in this briefing document.

Study HPV-013

Comparison of seroconversion rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies between HPV-013 subjects (10-14 year olds) and HPV-001 subjects (15-25 year olds): The majority (84.9%) of the 383 subjects selected from the HPV-001 study (HPV-001 group) were seronegative for both HPV-16 and HPV-18 antigens before vaccination. In both groups, all initially seronegative subjects had seroconverted for both antigens after the third vaccine dose. The GMT values in the HPV-013 HPV vaccine group were higher for anti-HPV-16 antibodies and anti-HPV-18 antibodies as measured by ELISA as compared to study HPV-001: 19882.0 EU/mL versus 4415.9 EU/mL for anti-HPV-16 antibodies, and, 8262.0 EU/mL versus 3471.8 EU/mL for anti-HPV-18 antibodies. The reverse cumulative distribution curves for anti-HPV-16 and anti-HPV-18 antibodies show that all subjects in the two studies had seroconverted at Month 7 but with higher antibody titers achieved by subjects enrolled in the study HPV-013. The GMTs for anti-HPV 16 and HPV-18 are shown for each age group in Tables 22 and 23 below.

Table 22 - HPV-013: Seropositivity rates and GMTs for HPV-16 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

		≥8 EU/mL	GMT	Min, Max
Group	**Timing**	**n/N**	**Value**	
HPV-013	**PRE**	40/670 (6.0%)	4.3	<8.0, 141.0
	PII(M2)	659/662 (99.5%)	4733.8	<8.0, 49477.0
	PIII)M7)	656/656 (100%)	20018.1	706.0, 244471.0
HPV-001	**PRE**	24/371 (6.5%)	4.3	<8.0, 30.0
	PIII)M7)	362/362 (100%)	4378.4	65.0, 110768.0

HPV-013 = HPV-16/18 L1/AS04 from study HPV-013; HPV-001 = HPV-16/18 L1/AS04 from study HPV-001
GMT = geometric mean antibody titre calculated on all subjects; N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range;
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 013, Table 34, p. 86

Table 23 - HPV-013: Seropositivity rates and GMTs for HPV-18 IGG ELISA antibodies by pre-vaccination status (ATP cohort for immunogenicity)

		≥7 EU/mL	GMT	Min, Max
Group	**Timing**	**n/N**	**Value**	
HPV-013	**PRE**	29/668 (4.3%)	3.8	<7.0, 89.0
	PII(M2)	659/661 (99.7%)	3745.2	<7.0, 47111.0
	PIII)M7)	655/655 (100%)	8359.4	567.0, 2000687.0
HPV-001	**PRE**	37/371 (10.0%)	3.9	<7.0, 33.0
	PIII)M7)	362/362 (100%)	3459.8	107.0, 51346.0

HPV-013 = HPV-16/18 L1/AS04 from study HPV-013; HPV-001 = HPV-16/18 L1/AS04 from study HPV-001
GMT = geometric mean antibody titre calculated on all subjects; N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with titre within the specified range;
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum; PII(M2) = Post Dose II (Month 2); PIII(M7) = Post Dose III (Month 7)
Source: STN 125259/0, CSR 013, Table 35, p. 87

Seropositivity rates and GMTs for anti-MPL antibodies: Of interest, the seropositivity rates and GMTs for anti-MPL antibodies by pre-vaccination status for a limited number of subjects in the immunogenicity subset are presented. At study entry, most of the subjects in the HPV group

and in the HAV group had anti-MPL antibody titers above or equal to the limit of quantification of the ELISA assay (----(b)(4)----). In subjects with detectable anti-MPL antibody titers before vaccination, there was an increase in GMT values following the third dose of HPV-16/18 vaccine compared to pre-vaccination levels. In the HAV group, there was no noticeable difference in anti-MPL antibody titres after Dose 2 and Dose 3 compared to the titer at study entry.

Immunogenicity conclusions for HPV-013:

- One month after the third dose, 100% of subjects had seroconverted for both HPV-16 and HPV-18 antigens in the HPV-013 HPV vaccine group with high GMT values.
- The Month 7 GMT values in the HPV-013 study (10 - 14 year olds) were more than 4-fold higher for anti-HPV-16 antibodies and more than 2-fold higher for anti-HPV-18 antibodies than those in the HPV-001 study (15 - 25 year olds).
- At study entry, most subjects in the HPV group and in the HAV group had anti-MPL antibodies. An increase in anti-MPL antibody titres in the HPV group was noticed after the second and third vaccine doses but not in the HAV group.

SAFETY RESULTS: HPV-008 and HPV-013

Table 24 - Study HPV-008 Safety Populations [CBER generated]

Cohort	AEs	Cervarix™	Havrix	Total
Total Vaccinated Cohort	SAEs, Deaths, NOCDs, NOADs, Pregnancy Outcomes	9319	9325	18644
Safety Diary Card Subset	Solicited AEs; Unsolicited AEs within 29 days of vaccination	3184	3187	6371

A population not included in this document is the ATP cohort for safety. This population included 8409 Cervarix™ recipients and 8431 Havrix recipients [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), and were not protocol violators].

Solicited symptoms and unsolicited symptoms (0-29 days) were presented for subjects in the safety diary card subset. Serious Adverse Events, Deaths, New Onset Chronic diseases, New Onset Autoimmune Diseases, and Pregnancy Outcomes were presented for the Total Vaccinated Cohort.

Table 25 - Study HPV-008: Demographics of Total Vaccinated Cohort
Summary of demographic characteristics (Total Vaccinated cohort)

		HPV N=9319	HAV N=9325	Total N=18644
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	20.0	20.0	20.0
	SD	3.1	3.1	3.1
	Median	20.0	20.0	20.0
	Min-Max	14.0-33.0	14.0-33.0	14.0-33.0
Region	Asia Pacific	3175 (34.1%)	3177 (34.1%)	6352 (34.1%)
	Europe	3224 (34.6%)	3224 (34.6%)	6448 (34.6%)
	Latin America	1388 (14.9%)	1386 (14.9%)	2774 (14.9%)
	North America	1532 (16.4%)	1538 (16.5%)	3070 (16.5%)
Race	Black	33 (3.6%)	360 (3.9%)	693 (3.7%)
	White/Caucasian	5120 (54.9%)	5098 (54.7%)	10218 (54.8%)
	Arabic/North African	10 (0.1%)	13 (0.1%)	23 (0.1%)
	East/South East Asia	2173 (23.3%)	2173 (23.3%)	4346 (23.3%)
	South Asian	8 (0.1%)	12 (0.1%)	20 (0.1%)
	Japanese	3 (0.0%)	3 (0.0%)	6 (0.0%)
	Hispanic	668 (7.2%)	662 (7.1%)	1330 (7.1%)
	Chinese	761 (8.2%)	753 (8.1%)	1514 (8.1%)

	Malay	1 (0.0%)	1 (0.0%)	2 (0.0%)
	Indian	4 (0.0%)	6 (0.1%)	10 (0.1%)
	Other*	238 (2.6%)	244 (2.6%)	482 (2.6%)

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects; n = number of subjects in a given category; Value = value of the considered parameter
% = n / Number of subjects with available results x 100; SD = standard deviation; * Other includes mainly mixed ethnicity, native American and native Canadian.; Source: STN 125259.0048, CSR 008, Table 24, p. 205

Compliance with the returning of safety diary cards was at least 95.4% after each dose in the HPV and HAV groups.

Solicited local adverse events in 7 days after vaccination (Safety Diary Card Subset): 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. 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. Redness at the injection site was reported by 43.8% and 27.6% of subjects in the HPV and HAV groups, respectively. Swelling at the injection site was reported by 42.0% and 19.8% of subjects, respectively. Grade 3 redness and swelling (>50 mm) were infrequently reported. 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).

Solicited general adverse events in 7 days after vaccination (SafetyDiary Card Subset): 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 was also higher in the HPV group compared to the HAV group. There was no increase in the proportion of subjects who developed a solicited general adverse event with successive doses of Cervarix™. The events were of short duration, and similar in the two groups. A very low percentage of subjects missed school or work because of these AEs (1.5% HPV, 1.3% HAV).

- **Fatigue** was reported by 57.6% and 53.6% of subjects in the HPV and HAV groups, respectively.
- **Myalgia** was reported by 52.2% and 44.9% of subjects in the HPV and HAV groups, respectively. Grade 3 myalgia was reported following 1.8% and 0.6% of doses, respectively. (95% CIs did not overlap).
- **Headache** was reported by 54.1% and 51.3% of subjects in the HPV and HAV groups, respectively.

***Unsolicited adverse events in 30 days after vaccination (Safety Diary Card Subset)*:** During the 30-day post-vaccination period, 42.5% and 43.6% of subjects reported at least one unsolicited symptom in the HPV and HAV groups, respectively. A similar percentage of subjects (7.6% in the HPV group and 6.9% in the HAV group) reported unsolicited symptoms assessed as grade 3.

- The most common unsolicited symptoms (≥1% of doses in both groups) were headache (6.8% HPV, 7.6% HAV); influenza (4.9% HPV, 5.6% HAV); gynaecological chlamydia infection (4.1% HPV, 4.4% HAV); nasopharyngitis (3.5% HPV, 3.4% HAV); pharyngolaryngeal pain (3.0% HPV, 2.7% HAV) and dizziness (2.8% HPV, 2.6% HAV).
- Injection site nodules were reported in 0.6% HPV and 0.1% HAV recipients; Injection site pruritus was reported by 0.9% HPV and 0.5% HAV recipients; dyspepsia in 0.3% HPV and 0% in HAV recipients; and infectiouos mononucleosis in 0.2% HPV and 0% HAV group.

Concomitant medication and vaccination in 30 days after vaccination (Safety Diary Card Subset): A similar percentage of subjects in both groups used concomitant medications, including anti-pyretics (32.7% HPV recipients in HPV group and 32.3% of HAV recipients) and antibiotics (21.5% HPV recipients and 21.8% HAV recipients) during the 30-day post-vaccination period.

Adverse Events Leading to Premature Discontinuation of StudyVaccine and/or Study (total Vaccinated Cohort): In total, eleven subjects in the HPV group (spontaneous abortion 5 months after dose 1; skin infection day 1 day after dose 2; and 9 deaths) and nine subjects in the HAV group (road traffic accident 8 months afer dose 3 and 8 deaths) withdrew due to an SAE, with none of these events reported as possibly related to vaccination according to the investigator. Five subjects in the HPV group (dry skin 9 days postdose 1; headache on days of dose 1 – possibly related per investigator; acne 18 days after dose 1; nausaea 17 days after dose 1; ovarian cyst 1 month after dose 1) and three subjects in the HAV group (hypoaethesia 12 days after dose 1; facial pain day of dose 1 – possibly related per investigator; gastroenteritis before vaccine) withdrew due to a non-serious adverse events.

Deaths at any time in study (Total Vaccinated Cohort): There were 9 deaths in the HPV group (0.1%) and 8 deaths in the HAV group (0.09%). These deaths are included in the overview of safety results.

Serious adverse events at any time during the study (Total Vaccinated Cohort): 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 (7.5% of subjects in each group). In a subgroup analysis of subjects who were DNA positive at baseline, there were 76/690 (11.0% [95% CI: 8.8, 13.6%]) Cervarix™ recipients with an SAE and 58/649 (8.9% [95% CI: 6.9, 11.4%]) Havrix recipients with an SAE, although the pattern of SAEs were similar in both subgroups.

New Onset Chronic Diseases at any time during the study (Total Vaccinated Cohort): Overall, the proportion of subjects experiencing a NOCDs (as assessed by GSK per list in Attachment 1) was similar in the HPV and HAV groups: 251 (2.7%) and 268 (2.9%) subjects, respectively. NOCDs were defined in a similar manner to study HPV-007. The most common NOCDs were asthma (0.4%) each group); urticaria (0.3% HPV subjects and 0.2% HAV subjects); hypersensitivity (0.2% HPV, 0.3% HAV); hypothyroidism (0.2% each group); and seasonal allergy (0.1% HPV and 0.2% HAV).

New Onset Autoimmune Diseases at any time during study (Total Vaccinated Cohort): NOADs were a subset of diseases within NOCDs considered to be of potential autoimmune etiology**.** Overall, the number of subjects experiencing an NOAD (as assessed by GSK) was similar in the HPV and HAV groups: 78 (0.8%) and 77 (0.8%) subjects, respectively. The most frequently reported NOAD was hypothyroidism, reported in 0.2% of each group.

Medically significant conditions prompting emergency room visits or physician visits (Total Vaccinated Cohort): The percentages of subjects reporting at least one medically significant AE prompting emergency room visits or physician visits within the 30-day follow-up period post-vaccination were similar in the two groups (31.8% HPV and 32.4% HAV). The most common medically significant conditions were: gynecological chlamydia infection (reported in (9.8%) subjects in the HPV group and 10.3% subjects in the HAV group); genito-urinary tract gonococcal infection (reported in 1.5% subjects in the HPV group and 1.7% subjects in the HAV group); and depression (reported in 1.5% subjects in the HPV group and 1.5% subjects in the HAV group.)

Pregnancy Outcomes are discussed for studies overall.

Study HPV-013 Safety Results

Table 26 - Study HPV-013 Safety Populations [CBER generated]

Cohort	AEs	Cervarix™	Havrix	Total
Total Vaccinated Cohort	Solicited AE; Unsolicited AEs; SAEs, Deaths, NOCDs, NOADs, Pregnancy Outcomes	1035	1032	2067

A population not included in this document is the ATP cohort for safety. This population included 1019 Cervarix™ recipients and 1012 Havrix recipients [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), and were not protocol violators].

Table 27 - Study HPV-013: Demographics of Total Vaccinated Cohort

		HPV N=1035	HAV N=1032	Total N=2067
Characteristics	Parameters or Categories	Value or n (%)	Value or n (%)	Value or n (%)
Age (years)	Mean	12.1	12.1	12.1
	SD	1.4	1.4	1.4
	Median	12.0	12.0	12.0
	Min-Max	10-15	10-14	10-15
Region	Asia Pacific	192 (18.6%)	193 (18.7%)	385 (18.6%)
	Europe	524 (50.6%)	522 (50.6%)	1046 (50.6%)
	Latin America	319 (30.8%)	317 (30.7%)	636 (30.8%)
Race	Black	6 (0.6%)	10 (1.0%)	16 (0.8%)
	White/Caucasian	571 (55.2%)	564 (54.7%)	1135 (54.9%)
	Arabic/North African	5 (0.5%)	1 (0.1%)	6 (0.3%)
	East/South East Asia	0 (0.0%)	3 (0.3%)	3 (0.1%)
	South Asian	0 (0.0%)	1 (0.1%)	1 (0.0%)
	Hispanic	315 (30.4%)	313 (30.0%)	628 (30.4%)
	Chinese	109 (10.5%)	109 (10.6%)	218 (10.5%)
	Other	29 (2.8%)	31 (3.0%)	60 (2.9%)

HPV = HPV-16/18 L1/AS04; HAV = Hepatitis A vaccine group; N = number of subjects; n = number of subjects in a given category
Value = value of the considered parameter; % = n / Number of subjects with available results x 100
SD = standard deviation; Source: STN 125259/0, CSR 013, Table 17, p. 64

Solicited local adverse events in the 7 days after vaccination (Total Vaccinated Cohort): Grade 3 pain and swelling was higher in HPV recipients as compared to HAV recipients when presented by dose and by subject, and 95% CIs did not overlap. There was an increase in the proportion of subjects with swelling with progressive doses of HPV vaccine (20.9% to 28.4%). There is a lower proportion of subjects with pain after doses 2 and 3 (66.6% and 65.9%, respectively) as compared to dose 1 (77.8%). Duration of pain (3.0 days in the HPV group and 2.0 days in the HAV group), redness and swelling (2.0 days for both symptoms) during the 7-day post-vaccination period were similar in the two groups. In addition, duration of Grade 3 symptoms was also generally of short duration.

***Solicited general symptoms in the 7 days after vaccination (Total Vaccinated Cohort)*:** The incidence of solicited general symptoms was higher following HPV-16/18 vaccine administration as compared to HAV vaccine administration. The pattern of adverse events was similar between both study groups with respect to the relative incidence, severity, and duration. However, a higher proportion of HPV recipients who over the course of the vaccination series experienced a solicited general adverse event as compared to HAV recipients. The 95% CIs do not overlap for all and grade 3 arthralgia; all fatigue; all and grade 3 myalgia. The proportions of subjects who developed a solicited general symptoms are presented in Table 28 below.

Table 28 - Study HPV-013: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period overall per dose and per subject (Total Vaccinated Cohort)

	HPV		HAV	
	Overall/subject			
Symptom	n/N	%	n/N	%
Arthralgia				
All	259/1029	**25.2%**	204/1027	**19.9%**
Grade 3	21/1029	**2.0%**	5/1027	**0.5%**
Fatigue				
All	499/1029	**48.5%**	434/1027	**42.3%**
Grade 3	40/1029	3.9%	30/1027	2.9%
Fever (º C) Axilla				
All	193/1029	18.8%	164/1027	16.0%
>39.0	19/1029	1.8%	14/1027	1.4%
Gastrointestinal				
All	265/1029	25.8%	253/1027	24.6%
Grade 3	26/1029	2.5%	22/1027	2.1%
Headache				
All	516/1029	50.1%	464/1027	45.2%
Grade 3	68/1029	6.6%	40/1027	3.9%
Myalgia				
All	509/1029	**49.5%**	340/1027	**33.1%**
Grade 3	57/1029	**5.5%**	13/1027	**1.3%**
Rash				
All	98/1029	9.5%	69/1027	6.7%
Grade 3	8/1029	0.8%	3/1027	0.3%
Urticaria				
All	70/1029	6.8%	55/1027	5.4%
Grade 3	9/1029	0.9%	6/1027	0.6%

Bolded proportions have non-overlapping 95% CIs.
n=number of events; N=number of subjects with data
Source: STN 125259/0, CSR 013, Table 25, p. 72-74

The duration (median number of days) of fever, headache, arthralgia, urticaria, myalgia, fatigue and rash during the 7-day post-vaccination period was similar in both groups. Fever lasted a median of one day in both groups, and the other symptoms lasted a median of two days in both groups. Grade 3 general symptoms were also of short duration in both treatment groups. The incidence of solicited general symptoms reported during the 7-day (Days 0-6) period following each dose and overall did increase with consecutive doses. No differences in maximum temperatures were identified between the HPV and the HAV group.

Unsolicited symptoms in the 30 days after vaccination (Total Vaccinated Cohort): Overall, 386 subjects reported 685 unsolicited symptoms after 535 doses of HPV-16/18 vaccine, and 427 subjects reported 698 unsolicited symptoms after 565 doses of HAV vaccine within the 30-day post-vaccination period. The proportions of subjects with at least one unsolicited symptom were similar in the treatment groups (37.3% HPV, 41.4% HAV). The proportions of subjects with an event in the specific SOC are also similar in the treatment groups, and all 95% CIs around the proportions overlap.

Table 29 - Study HPV-013: Percentage of subjects reporting the occurrence of unsolicited symptoms classified by MEdDRA Primary System Organ Class, within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

	HPV N-1035	HAV N=1032
Primary System Organ Class	**n(%)**	**n(%)**
At least one symptom	**386 (37,3%)**	**427 (41.4%)**
Blood and lymphatic system disorders	3 (0.3%)	4 (0.4%)
Cardiac disorders	2 (0.2%)	1 (0.1%)

Ear and labyrinth disorders	10 (1.0%)	10 (1.0%)
Endocrine disorders	1 (0.1%)	3 (0.3%)
Gastrointestinal disorders	28 (2.7%)	38 (3.7%)
General disorders and administration site conditions	51 (4.9%)	39 (3.8%)
Hepatobilary disorders	0 (0.0%)	1 (0.1%)
Immune system disorders	5 (0.5%)	7 (0.7%)
Infections and infestations	226 (21.8%)	240 (23.3%)
Injury, poisoning and procedural complications	21 (2.0%)	28 (2.7%)
Investigations	1 (0.1%)	3 (0.3%)
Metabolism and nutrition disorders	7 (0.7%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	22 (1.3%)	16 (1.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	0 (0.0%)	1 (0.1%)
Nervous system disorders	54 (5.2%)	62 (6.0%)
Psychiatric disorders	2 (0.2%)	4 (0.4%)
Renal and urinary disorders	1 (0.1%)	1 (0.1%)
Reproductive system and breast disorders	23 (2.2%)	26 (2.5%)
Respiratory, thoracic and mediastinal disorders	67 (6.5%)	54 (5.2%)
Skin and subcutaneous tissue disorders	28 (2.7%)	27 (2.6%)
Surgical and medical procedures	5 (0.5%)	7 (0.7%)
Vascular disorders	4 (0.4%)	2 (0.2%)

Source: STN 125259/0, CSR 013, Supplement 23, p. 121

Concomitant medication (Total Vaccinated Cohort)*:* There was no increase in need for comcomitant medications with progressive doses, and the proportions of subjects taking concomitant medications, including anti-pyretics (25.9% HPV subjects, 23.3% HAV subjects) and antibiotic (11.7% HPV subjects and 10.9% HAV subjects), was similar.

Adverse Events Leading to Premature Discontinuation of StudyVaccine and/or Study (Total Vaccinated Cohort): There were no withdrawals due to AEs in the HPV group. Two subjects in the HAV group withdrew from the study due to non-serious adverse events, one subject because of pain ay the injection site afer dose 1; and one with joint swelling prior to dose 3 of HAV.
Serious Adverse Events (Total Vaccinated Cohort): The proportions of subjects with an SAE up to Month 7 were similar in both treatment groups overall (11 or 1.5% in the HPV group, and 13 or 1.3% in the HAV group). The risk difference did not reach statistical significance (Risk difference = 0.20 [95% CI: -0.78, 1.20%]. Of note, one subject in the HPV group and no subject in the HAV group experienced syncope, and the risk difference did not reach statistical significance. Through Month 24, 32 subjects in the HPV group reported 46 SAEs, and 29 subjects in the HAV group reported 33 SAEs. Over the entire study period (Months 0-24), only one SAE was reported as related to vaccination. This SAE, which occurred in the HAV group, was an aminotransferases increase in an 11 year old subject who experienced a urinary tract infection two days post-dose 3. The most common SAEs reported throughout the entire study period were abdominal pain (HPV group: 6 subjects, 0.6%; HAV group: none), appendicitis (HPV group: 1 subject, 0.1%; HAV group: 5 subjects, 0.5%).

Deaths (Total Vaccinated Cohort): There were no fatalities reported during the study (through Month 24).

New onset of chronic diseases (Total Vaccinated Cohort): Overall 46 subjects reported 47 AEs classified as NOCD according to GSK assessment. In the HPV group 25 subjects reported 26 events (2.4% of subjects) and in the HAV group 21 subjects reported 21 events (2.0% of subjects). The most frequently identified NOCD were rhinitis allergic (reported by 8 subjects in

the HPV group and by 5 subjects in the HAV group), asthma (reported by 4 subjects in the HPV group and by 3 subjects in the HAV group), hypersensitivity (reported by 4 subjects in the HPV group and by 3 subjects in the HAV group) and chronic urticaria (reported by 4 subjects in the HPV group and by 1 subject in the HAV group). During the entire study period up to Month 24, a similar number of subjects reported NOCDs based on GSK assessment in the HPV (42 subjects, 4.1%) and HAV (35 subjects, 3.4%) groups. The most common NOCDs reported throughout the entire study period were asthma (HPV group: 10 subjects, 1.0%; HAV group: 5 subjects, 0.5%), allergic rhinitis (HPV group: 10 subjects, 1.0%; HAV group: 6 subjects, 0.6%), hypersensitivity (HPV group: 6 subjects, 0.6%; HAV group: 3 subjects, 0.3%) and urticaria (HPV group: 4 subjects, 0.4%; HAV group: 2 subjects, 0.2%).

Medically significant conditions prompting emergency room visits or physician visits (Total Vaccinated Cohort): The percentages of subjects reporting at least one medically significant AE prompting emergency room visits or physician visits within the 30-day follow-up period post-vaccination were similar in the two groups (12.6% of subjects in the HPV group and 15.5% of subjects in the HAV group). During the entire study period to Month 24, the number of subjects reporting at least one medically significant event was similar in the HPV group (256 subjects reporting 419 events, 24.7% subjects) compared to the HAV group (270 subjects reporting 386 events, 26.2% subjects). The most frequently reported medically significant AEs during the entire follow-up period were bronchitis, abdominal pain, influenza, headache, asthma and acne. Abdominal pain was more frequently reported in the HPV group (1.6%) than in the HAV group (0.6%), while the opposite was observed for influenza (0.8% vs. 1.6%). The incidences of bronchitis (1.8% vs. 1.5%), headache (0.9% vs. 1.1%), asthma (1.1% vs. 0.7%) and acne (0.7% vs. 1.1%) were similar in the HPV and HAV groups, respectively. The percentages of subjects reporting at least one medically significant AE prompting emergency room visits or physician visits starting from Day 30 post-vaccination were similar in the two groups (8.3% of subjects in the HPV group and 8.4% of subjects in the HAV group).

Clinical Laboratory Evaluations (Total Vaccinated Cohort): At study entry and at Months 2 and 7, the hematological and biochemical parameters were evaluated in all subjects. For one subject who had laboratory tests done following a urinary tract infection that was reported as an SAE, the ALT levels were above the normal range (one of the SAEs). For most of the subjects in both groups the hematological and biochemical parameters were within the normal ranges at study entry and remained as such after each vaccine dose. Post Dose 3, the percentage of subjects remaining in the normal range for RBC, Hct, Platelets, WBC, differential, ALT, and Cr were generally > 90% for both groups, with similar proportions in each group. For each parameter, the percentage of subjects outside normal ranges was low and similar in the two groups.
Pregnancy: During the active phase of the study (up to Month 7), three pregnancies were reported (two subjects in the HAV group and one subject in the HPV group). During the entire study period from Month 0 to Month 24, a total of 16 pregnancies were reported, i.e., for 12 subjects in the HPV group and 4 subjects in the HAV group. Overview of pregnancy outcomes is discussed in all studies combined.

OVERVIEW OF SAFETY DATA ACROSS STUDIES
Several safety issues were identified in the review of the original BLA for Cervarix™. Because some studies were ongoing, with need to preserve blind, CBER had some concerns: The overall presentation of deaths across studies; adverse events related to potential neuroinflammtory etiology; adverse events of the musculoskeletal system related to potentially autoimmune etiology; cases of Grave's disease in the studies and appropriate testing for homogeneity; presentation of congenital anomalies across studies; and an imbalance noted in the rate of spontaneous abortions. During the original review, GSK prepared a meta-analysis of events of

neuroinflammatory events after discussion with CBER statisticians. The meta-analysis also assessed vaccines which contained monophosphoryl lipid A.

The events of specific interest were neuroinflammatory and musculoskeletal, and the data for these events were reviewed by an expert panel of neurologists and a panel of rheumatologists, respectively. With respect to pregnancy outcomes, congenital anomalies from the clinical trials program were reviewed by an expert panel of teratologists/geneticists. In addition, in response to a request by the Data Safety Monitoring Board (DSMB) having oversight for Study HPV-009, the National Cancer Institute (NCI) performed an independent analysis of spontaneous abortions data inclusive of data from Studies HPV-008 and HPV-009.

Common solicited and unsolicited adverse events were presented from the time of the original submission of the BLA in 3/07 because the time periods for these adverse events were 7- and 30-days after each vaccination. GSK prepared an update of safety through 8/31/08 for deaths, SAEs, pregnancy outcomes and abnormalities in children born to vaccinees, medically significant adverse events, study discontinuations due to adverse events, repeat meta-analysis of neuroinflammatory and musculoskeletal events, and updated pooled safety analysis of adverse events classified as NOCDs and NOADs. Additionally, post-marketing safety updates from foreign countries where Cervarix™ is licensed (including countries in Asia, Australia, Europe, and South America) were provided through 11/17/08, and more recently, through 4/09.

Overview of deaths: GSK provided a breakdown of deaths in each treatment group in JMP datasets. From the tables provided, there were 18 subjects in the control group and 20 subjects in the HPV group who died during all studies. The number and proportion of Cervarix™ recipients who died (20/33623 or 0.06%) was similar to the number of control recipients (18/23700 or 0.08%). Please see Table 33 in Appendix.

Overview of Serious Adverse Events: For the analysis of SAEs and deaths, there were differences in number of subjects and mean duration of follow-up between the HPV group and Control group (31,472 female subjects and 26.2 months in the HPV group and 23,700 subjects and 29.9 months in the Control group). All studies in which Cervarix™ was administered were pooled together for the HPV group thus pooling subjects enrolled in uncontrolled studies as well as controlled studies. When considering the individual conrolled studies included in the BLA (specifically HPV-001/007, HPV-008, and HPV-013) there were no apparent imbalances in the rates of serious adverse events throughout each individual study as noted earlier in this document. **Please see the safety analyses in Tables 34, 35, 36 and 37 in attachment 5.**

Medically Significant Adverse Events: MsAEs were defined as adverse events prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or serious adverse events 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. The mean follow-up time for the reporting of medically significant adverse events in the HPV(N=15,469) and Pooled Control(N=13,228) groups was comparable: 34.4 months and 35.7 months in the HPV and Pooled Control groups respectively, a difference of 4 %. The percentage of subjects reporting at least one MsAE in the HPV and Pooled Control groups was 14.4% and 15.5% respectively in the vaccination period (0-7 Months) and 29.0% and 31.4% respectively in the full observation period.

The most commonly reported MsAE was gynecological chlamydia infection reported at a lower frequency of reports in the HPV group as compared to the pooled control group: 2.56% (95% CI

2.32; 2.82) versus 3.11% (95% CI 2.82; 3.42) for the post-vaccination period. For other individual terms, there were no significant differences in the reporting rates between the HPV and control groups.

The proportions of medically significant adverse events were similar in each age groups 10-14, 15-25 and >25 when compared directly. The most commonly reported MsAE in 10-14 year-olds was bronchitis with a similar rate between the HPV-16/18 group (1.2%) and the HAV360 group (1.1%) during the vaccination period and 2.1% and 1.6% respectively for the full observation period.

In 15-25 year-olds, the most commonly reported MsAE was gynecological Chlamydia infection. The frequency was lower in the HPV-16/18 vaccine group (3.6%) than the HAV720 control group (4.4%) during the vaccination period and 8.3% and 10.3% respectively for the full observation period

Adverse Events/Serious Adverse Events leading to discontinuation from studies: In studies submitted to the BLA, from a total of 29,953 subjects included in the pooled safety analysis, 72 subjects were withdrawn due to an AE or SAE (43 subjects received Cervarix™ [0.27%] and 29 subjects received control [0.21%]). A total of 31 subjects withdrew due to an SAE (14 subjects received Cervarix™ [0.09%] and 17 subjects received control vaccine [0.12%]). Of these, sixteen events were fatal events and the other 15 subjects withdrew due to other SAEs, none of which were considered as causally related to vaccination by the study investigator:

- 7 subjects received Cervarix™: the withdrawals were due to multiple sclerosis, a prolapsed vertebral disc, moderate dermatological infection, invasive ductal carcinoma stage I (left breast), cervical adenocarcinoma, and spontaneous abortion (2 subjects);
- 8 subject received Havrix (360 EL.U. HAV antigen and 250µg Al(OH)3 per 0.5 mL dose): enteritis, abdominal pain, renal abscess, anorexia nervosa, cervical carcinoma stage 0, malignant neoplasm, uterine procidentia, and multiple trauma following an automobile crash;

There were in total 41 other subjects who experienced non-serious adverse events that led to study withdrawal, of which 29 subjects received Cervarix™ (0.18%) and 12 subjects received control vaccine or placebo (0.09%).

New Onset of Chronic Diseases and New Onset of Autoimmune Diseases: For the vaccination period (Month 0 to Month 7), the overall reporting rates of NOCDs in subjects that received HPV-16/18 vaccine was similar to that observed in subjects who received control: 1.2% (95% CI: 1.0; 1.4) in the HPV group and 1.0% (95% CI: 0.9; 1.3) in the pooled control group. For the entire reporting period, the percentage of subjects with reports of NOCDs were 2.4% (95% CI: 2.2; 2.7) in the HPV group and 2.6% (95% CI: 2.4; 2.9) in the pooled control group.

The most commonly reported NOCDs were asthma, hypersensitivity and urticaria, as seen in the initial pooled safety analysis of NOCDs. The percentage of subjects reporting these events was low and similar among the treatment groups.

There were no differences between the HPV group and the control groups in reporting of NOCDs when considering subjects of each age group.

To evaluate the incidence of new onset of autoimmune diseases (NOADs), a list of potential autoimmune events, which excluded allergy related events or isolated signs and symptoms and events not considered as strictly of autoimmune origin, was approved by the IDMC supervising the Studies HPV-008, HPV-013 and HPV-015. Based on this list (See Attachment 1), a GSK

Biologicals physician reviewed the adverse events that were considered NOCDs for the classification of events considered as new onset of autoimmune disease. There were no differences in the overall incidences of potential autoimmune diseases with new onset reported in the HPV group compared to the control groups or the pooled control group for either the vaccination period or the full observation reporting period.

The two most frequently reported NOADs were hypothyroidism, with three subjects in the HPV/[15-25] age group (< 0.1%) versus one subject in the HAV720/[15-25] age group (< 0.1%), and goiter with one subject in the HPV/[15-25] age group (< 0.1%) versus three subjects in the HAV720/[15-25] age group (< 0.1%).

The most frequently reported potential autoimmune disease with new onset was hypothyroidism with 22 subjects in the HPV/[15-25] age group (0.2%) versus 20 subjects in the HAV720/[15-25] age group (0.2%), three subjects in the ALU/[15-25] age group (0.8%) and one subject in the HPV/[25+] age group.

Pregnancies and pregnancy outcomes: The database includes 19,871 subjects that received at least one dose of Cervarix™ and 17,548 subjects that received at least one dose of control, depending on their age at enrolment.

Table 30 - Number of subjects vaccinated and reported pregnancies during the entire study period, by group in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

	HPV	Alu	HAV 360	HAV 720	Pooled control	Total
Number of subjects vaccinated	19,871	3454	1032	13062	17548	37419
Number of reported pregnancies	3696	380	10	3190	3580	7276

HPV = HPV-16/18 vaccine group (Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023)
ALU = Al(OH)3 control group (Studies HPV-001, 003, 007, 015)
HAV360 = Hepatitis A control group containing 360 EL.U. hepatitis A antigen per dose (Studies HPV-013, 013 Ext)
HAV720 = Hepatitis A control group containing 720 EL.U. hepatitis A antigen per dose (Studies HPV-008, 009)
Pooled Control = ALU, HAV360 and HAV720 groups
Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
Source: STN 125259.48, Supplemental safety update, Table 34, p. 107

Overview of number of subjects with pregnancies reported: Of the 7,276 subjects with pregnancies reported, 761 subjects (10.46%) became pregnant around the time of vaccination (i.e. LMP occurred from 30 days before up to 45 days after vaccination). Overall, the age of subjects included in this analysis ranged from 13 to 50 years.

Analysis of pregnancy outcomes overall

Table 31 - Pregnancy outcomes overall for the total number of pregnancies in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV N=3696	HAV 720 N=3190	Alu N=380	HAV 360 N=10	Pooled control N=3580	Total N=7276
Normal infant	2300 (62.23%)	2012 (63.07%)	221 (58.16%)	7 (70.0%)	2240 (62.57%)	4540 (62.40%)
Premature birth	73 (1.98%)	51 (1.60%)	9 (2.37%)	2 (20.0%)	62 (1.73%)	135 (1.86%)
Abnormal infant other than congenital anomaly	105 (2.84%)	106 (3.32%)	8 (2.11%)	0 (0.0%)	114 (3.18%)	219 (3.01%)
Elective termination	216	194	22	1	217 (6.06%)	433

	(5.84%)	(6.08%)	(5.79%)	(10.0%)		(5.95%)
Therapeutic sbortion	4 (0.11%)	1 (0.03%)	3 (0.79%)	0 (0.0%)	4 (0.11%)	8 (0.11%)
Ectopic pregnancy	22 (0.60%)	15 (0.47%)	6 (1.58%)	0 (0.0%)	21 (0.59%)	43 (0.59%)
Spontaneous abortion	408 (11.04%)	323 (10.13%)	65 (17.11%)	0 (0.0%)	388 (10.84%)	796 (10.94%)
Stillbirth	20 (0.54%)	17 (0.53%)	2 (0.53%)	0 (0.0%)	19 (0.53%)	39 (0.54%)
Congenital anomaly	30 (0.81%)	22 (0.69%)	6 (1.58%)	0 (0.0%)	28 (0.78%)	58 (0.80%)
Lost to follow-up	24 (0.65%)	24 (0.75%)	1 (0.26%)	0 (0.0%)	25 (0.70%)	49 (0.67%)
Not applicable	4 (0.11%)	3 (0.09%)	0 (0.0%)	0 (0.0%)	3 (0.09%)	7 (010%)
Pregnancy ongoing	490 (13.26%)	422 (13.23%)	37 (9.74%)	0 (0.0%)	459 (12.82%)	949 (13.04%)

N = number of pregnancies with LMP during the entire study period; n = number of pregnancies in a given category; Value = value of the considered parameter; % = n / N x 100; Twin pregnancies counted as one pregnancy
Spontaneous abortion includes missed abortion; Not applicable: e.g. mole, trophoblastic tumor
Source: STN 125259.48, Supplemental safety update, Table 37, p. 111

Pregnancies were assessed overall by age groups. The majority of subjects who became pregnant were 15-25 year old females: of those, 10.62% the HPV group, 10.14% in the HAV group, and 10.71% of the aluminum hydroxide group experienced a spontaneous abortion. In women 25+ years of age, 19.05% in the HPV group and 23.91% of aluminum hydroxide group experienced a spontaneous abortion. From the data presented, the rates of spontaneous abortion were higher in older women in the HPV and ALU groups. It is possible that the higher proportion of spontaneous abortions overall for the aluminum hydroxide group may be related to the results in the older women.
When completed pregnancies were considered, the spontaneous abortion rates in the HPV, HAV 720 and Alu groups were 12.8%, 11,8% and 19.0% respectively.

Table 32 - Pregnancy outcomes overall for the completed pregnancies in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV N=3178	HAV 720 N=2741	Alu N=342	HAV 360 N=10	Pooled control N=3093	Total N=6271
Normal infant	2300 (72.37%)	2012 (73.40%)	221 (64.62%)	7 (70%)	2240 (72.42%)	4540 (72.40%)
Premature birth	73 (2.30%)	51 (1.86%)	9 (2.63%)	2 (20%)	62 (2.0%)	135 (2.15%)
Abnormal infant other than congenital anomaly	105 (3.30%)	106 (3.87%)	8 (2.34%)	0	114(3.69%)	219 (3.49%)
Elective termination	216 (6.80%)	194 (7.08%)	22 (6.43%)	1 (10%)	217 (7.02%)	433 (6.90%)
Therapeutic sbortion	4 (0.13%)	1 (0.04%)	3 (0.88%)	0	4 (0.13%)	8 (0.13%)
Ectopic pregnancy	22 (0.69%)	15 (0.55%)	6 (1.75%)	0	21 (0.68%)	43 (0.69%)
Spontaneous abortion	408 (12.84%)	323 (11.78%)	65 (19.01%)	0	388 (12.54%)	796 (12.69%)
Stillbirth	20 (0.63%)	17 (0.62%)	2 (0.58%)	0	19 (0.61%)	39 (0.62%)
Congenital anomaly	30 (0.94%)	22 (0.80%)	6 (1.75%)	0	28 (0.91%)	58 (0.92%)

Completed pregnancies: number of pregnancies with a known outcome (i.e. excluding ongoing pregnancies, lost to follow-up and pregnancies categorized as "not applicable")
Source: STN 125259.48, Supplemental safety update, Table 39, p. 113

For completed pregnancies in the 15-25 year old age group, of those, 12.29% in the HPV group, 11.81% in the HAV group, and 10.99% of the aluminum hydroxide group experienced a spontaneous abortion. In women 25+ years of age, 23.67% in the HPV group and 29.14% of the aluminum hydroxide group experienced a spontaneous abortion.

Analysis of pregnancies around vaccination

There were a total of 761 pregnant subjects who had their LMP around vaccination (defined as LMP from 30 days before until 45 days after vaccination). Consistent to what has been observed

in the analyses of pregnancies around vaccination made for the initial BLA submission (March 2007) and the CR letter responses (April-May 2008), the rate of spontaneous abortion in this subgroup analysis showed an imbalance between the HPV, HAV, and ALU group with rates of 54/396 (13.6%), 28/321 (8.7%), 7/43 (16.8%) and 36/365 (9.6%) for the HPV, HAV 720 , Alu and Pooled control groups respectively.

When analyzed by age groups, of women who became pregnant, the imbalance is noted in the 15-25 year old age group: 13.37% in the HPV group, 8.78% in the HAV group, and 8.33% in the ALU group experienced a spontaneous abortion. In women 25+ years of age who became pregnant, 19.05% in the HPV group and 19.35% in the ALU group experienced a spontaneous abortion.

Completed pregnancies reported with LMP around vaccination: From the 761 pregnant subjects who had their LMP around vaccination, 751 had a known outcome (i.e. completed pregnancies). These observations are very similar to those made in the analysis for all pregnancies in subjects who had their LMP around vaccination.

Table 33 - Pregnancy outcomes around vaccination for the completed pregnancies in Studies HPV-001, 003, 004, 005, 008, 009, 012, 013, 014, 015, 016 (Total vaccinated cohort, data lock-point of August 31, 2008)

Pregnancy outcomes	HPV N=392	HAV 720 N=316	Alu N=42	HAV 360 N=1	Pooled control N=359	Total N=751
Normal infant	258 (65.82%)	231 (73.10%)	22 (52.38%)	0	253 (70.47%)	511 (68.04%)
Premature birth	10 (2.55%)	6 (1.90%)	2 (4.76%)	1 (100%)	9 (2.51%)	19 (2.53%)
Abnormal infant other than congenital anomaly	20 (5.10%)	16 (5.06%)	1 (2.38%)	0	17 (4.74%)	37 (4.93%)
Elective termination	39 (9.95%)	27 (8.54%)	8 (19.05%)	0	35 (9.75%)	74 (9.85%)
Therapeutic sbortion	1 (0.26%)	1 (0.32%)	0	0	1 (0.28%)	2 (0.27%)
Ectopic pregnancy	2 (0.51%)	1 (0.32%)	0	0	1 90.28%)	3 (90.40%)
Spontaneous abortion	54 (13.78%)	28 (8.86%)	7 (16.67%)	0	35 (9.75%)	89 (11.85%)
Stillbirth	1 (0.26%)	2 (0.63%)	1 (2.38%)	0	3 (0.84%)	4 (0.53%)
Congenital anomaly	7 (1.79%)	4 (1.27%)	1 (2.38%)	0	5 (1.39%)	12 (1.60%)

Source: STN 125259.48, Supplemental safety update, Table 43, p. 118

When analyzed by age groups, of completed pregnancies, the imbalance is noted in the 15-25 year old age group: 13.51% in the HPV group, 8.92% in the HAV group, and 8.33% in the ALU group experienced a spontaneous abortion. Of completed pregnancies in women 25+ years of age, 19.05% in the HPV group and 20.0% in the ALU group experienced a spontaneous abortion.

The overall rates of spontaneous abortion (8.96% overall rate) from the updated analysis were similar between the HPV group (8.97%) and the HAV720 control group (8.66%) and lower than that reported for ALU control group alone (12.18%). No cases were reported in the HAV360 control group. As mentioned above, this difference across groups might be explained by the age distribution in the studies using either ALU placebo control (including subjects of 26 years old and above from Study HPV-015) or HAV360 control (including subjects of 10-14 years old), and the higher risk of miscarriage with increasing maternal age.

Analysis of spontaneous abortions: In the clinical trial program, information collected on pregnancies takes into account the date of the last menstruation period (LMP) and not the estimated date of conception, as the latter is considered to be less reliable. The date of conception is usually not known and ovulation varies in timing from onset of menstruation among different women and from cycle to cycle. GSK indicated the estimated date of conception was calculated as the LMP + 14 days assuming that ovulation/conception occurs on cycle day 14 in the average 28-day menstrual cycle. In this pooled analysis, the HPV group is based on data from all studies, while the HAV720 group is only based on Studies HPV-008 and HPV-009.

Table 34 - Percentage of spontaneous abortions of completed pregnancy outcomes in Studies HPV-001, 003, 004, 005, 007, 008, 009, 012, 012 Ext, 013, 013 Ext, 014, 014 Ext, 015, 016 and 023 (Total vaccinated cohort, data lock-point of August 31, 2008)

	HPV	HAV 720	Alu	HAV 360	Pooled control	Total
Overall pregnancy outcomes	12.84%	11.78%	19.01%	0%	12.54%	12.69%
Pregnancy outcomes around vaccination	13.78%	8.86%	16.67%	0%	9.75%	11.85%

Source: STN 125259.48, Supplemental safety update, Table 47, p. 124

Table 35 - Reporting rate of spontaneous abortions with LMP around vaccination period by analysis (Total vaccinated cohort)

	HPV	HAV 720	Alu	HAV 360
BLA submission March 2007*	23/210 (11.0%)	10/175 (5.7%)	4/29 (13.8%)	0/1 (0%)
Updated pooled analysis DLP 8/31/08†	54/396 (13.6%)	28/321 (8.72%)	7/43 (16.3%)	0/1 (0%)

*Studies HPV-001, HPV-003, HPV-004, HPV-005, HPV-008 (interim analysis), HPV-012, HPV-013, HPV-014, HPV-015 (interim Month 7 safety analysis), HPV-016.; †Studies HPV-001, HPV-003, HPV-004, HPV-005, HPV-008, HPV-009, HPV-012, HPV-013, HPV-014, HPV-015, HPV-016.
N= number of total pregnancies with LMP around vaccination period; n= number of spontaneous abortion with LMP around vaccination period; Note: all reporting rates based on 'total' number of pregnancies around vaccination
Source: STN 125259.48, Supplemental safety update, Table 48, p. 124

Comparison between induced and spontaneous abortions: In view of the imbalance observed in some analyses for both the spontaneous and induced abortions, further assessment was performed to determine whether there were any trends by country on the distribution of these two pregnancy outcomes. There were a total of 1,237 abortion cases reported up to August 31, 2008 in studies included in this updated analysis, of which 796 were classified as spontaneous abortion and 433 as induced abortions (i.e., outcome "elective termination").

An overview of the overall rates of spontaneous versus induced abortions by country was provided by GSK. In some countries, when all pregnancies are considered, the rates of spontaneous abortions exceed those of induced abortions, including Brazil [0.76 vs. 0.08], Costa Rica [4.81, 0], Mexico [0.81 vs. 0.07] and the Philippines [1.33 vs. 0.34]. Abortion is reportedly illegal in these countries, unless the woman's health is at risk or the pregnancy is due to rape, and it is postulated (but not proven) that reporting rates for the specific terms in certain countries may not accurately reflect the actual rate. In other countries these rates are either comparable or higher for the induced abortions. When pregnancies around vaccination are considered, the differences are also noted in the countries noted above, where spontaneous abortions exceed induced abortions [0.53 vs. 0 in Brazil, 6.04 vs. 0 in Costa Rica, 1.45 vs. 0 in Mexico, and 1.45 vs. 0.92 in the Philippines.]

At the request of the HPV-009 Data Safety Monitoring Board (DSMB), an analysis of spontaneous abortion rates in the pooled pregnancy datasets of studies HPV-008 and HPV-009 was performed. These studies were assessed because these are two of the largest studies in the

Cervarix™ development program, including over 25,000 women. The two trials are similarly designed, using double blind, randomized methodology and the same control vaccine (Hepatitis A vaccine). The pregnancies reported in the Studies HPV-008 and HPV-009 account for 87.9% of pregnancies reported in the HPV program.

The analysis was performed by an unblinded trial statistician from the NCI in consultation with two experts in the epidemiology of reproductive health, and according to a prespecified statistical plan developed by NCI, reviewed by GSK and approved by the DSMB overseeing the HPV-009 trial. The analysis plan was designed specifically to address the issues of timing of vaccine administration relative to pregnancy onset and its possible role in risk for spontaneous abortion, with careful control of Type I errors (false positive rate).

Because the mechanisms by which the vaccine could potentially affect pregnancies are unknown, the specific window of time between conception and vaccination for pregnancies that might be at risk is unknown as well. A permutation test was used maintaining Type 1 error with only small loss of power regardless of the true window of increased risk. The choice of permutation test was based on the fact that the external scientific experts could not agree on a specific time window in which an excess risk of spontaneous abortions could be expected due to vaccination, since the expert consultants stated that it is impossible to identify a gestation age interval *a priori* before and during early pregnancy during which any effect on spontaneous abortion risk is most likely to occur.

The 1-sided p-value for the pre-specified primary analysis by permutation testing of the combined data was 0.16, well above the standard critical value of 0.025 for a 1-sided test. Overall there was no significant increase in the rate of spontaneous abortions in women having been vaccinated with Cervarix™ compared to control (HAV 720) when the onset of pregnancy, defined as the estimated date of conception (14 days following date of onset of last menstrual period), occurred anytime from 0 to 2 years following vaccination.

A secondary descriptive analysis was performed evaluating the rates of spontaneous abortions for different time intervals (day of pregnancy onset after nearest vaccination). When restricting to pregnancies that began in the first 3 months after vaccination (i.e., with onset between 0 and 89 days from nearest vaccination), there was a higher rate of spontaneous abortion in the HPV-16/18 vaccine arm (15.4%) compared to the control arm (9.6%). For pregnancies that began beyond 90 days after vaccination, there was no apparent difference between groups (11.3% vs. 11.1%). This secondary analysis was considerd exploratory.

Based on the available data, the NCI concluded the following:

- The primary test of the effect of vaccination with HPV-16/18 vaccine on risk of spontaneous abortion was not close to significance.
- The spontaneous abortion rate was higher (15.4% vs. 9.6%) in the HPV-16/18 vaccine arm than the control arm for pregnancies with onset within the 90 days following vaccination.
- Most (58.3%) of the miscarriages occurred between 7 and 12 weeks of gestation, consistent with published literature.
- There was no decrease in the incidence of total pregnancies or live births in the HPV-16/18 vaccine arm overall [including the period of 3 months after vaccination].
- These data do not establish a relationship between HPV vaccination and spontaneous abortion risk but are insufficient to rule out a small effect in pregnancies conceived in the 3 months immediately after vaccination.

GSK reported that the NCI presented this analysis to the IDMC of the HPV-008 study. The IDMC provided the following statement:
"Following further consideration of the spontaneous abortion analysis and new information presented today, the IDMC concludes:

1. Overall, the IDMC finds no evidence for a causal association between HPV vaccine and spontaneous abortion.
2. However, given the uncertainty of the data, particularly with respect to the diagnosis of pregnancy, we cannot exclude a possible association between HPV vaccine and spontaneous abortion in the first 90 days following vaccination and onset of pregnancy.
3. The IDMC is reassured that the two planned Phase IV studies in Scotland and Finland can potentially provide data to illuminate the uncertainty at 0-90 days. Non-randomized post-marketing surveillance programs are less likely to be informative."

Cases of spontaneous abortion occurred in women from 0->1200 days from time of vaccination. The dataset which included all spontaneous abortions was reviewed by CBER, and searched for events which occurred in the time window from vaccination to EDC within -30 to +45 days. In this subset, the distribution of time of spontaneous abortions was similar in the treatment groups, CBER noted that the times at which the spontaneous abortions occurred were similar (mean app. 10 weeks gestation). CBER also notes that the proportions of spontaneous abortions which occurred were within the reported background rates which are reported for such events in the general population, although the estimates can range from 9-44% in the literature. When compared to the spontaneous abortion rates in the Gardasil database, the rates in each group are actually lower than those reported for subjects participating in the Gardasil studies (either in the Gardasil group or the control group), although no imbalance was noted between the treatment groups in the time period -30 to +30 days from time to vaccination to EDC in the Gardasil dataset, nor in the overall rates. Neither development program studied pregnancy in a controlled manner, and populations were not identical. Although there is no definitive indication that there is an enhanced risk of spontaneous abortions with use of Cervarix™, and overall rates of spontaneous abortion are low in the studies, and there may be confounding due to underreporting of pregnancy losses as spontaneous, a post-marketing enhanced pregnancy registry will be conducted to study this issue.

Stillbirths: The number of subjects who became became pregnant and in which the child was stillborn is approximately the same in each group across studies as noted above. There were 19 such events in the pooled control group and 20 such events in the HPV 16/18 group. There was no apparent imbalance in number of stillbirths. When reviewing the times from vaccination to EDC, most were remote from the time of vaccination, and there was no apparent difference between HPV and control groups as to interval between vaccination and EDC.

Congenital anomalies:

Among the 60 cases, no specific pattern or cluster of type of defects was identified. The three categories of defects most frequently reported were related to isolated cardiovascular defects (10 cases), central nervous system defects (9 cases) and limb defects (9 cases). In review of the cases of congenital anomalies, no specific pattern was identified.

GSK reported that the frequency is expressed as the number of cases with congenital anomalies among completed pregnancies per 100. The reported frequency of these events in the studies included in the extended pooled analysis of pregnancy outcomes was 0.96 reports per 100 completed pregnancies. Of these, there were:

- 30 subjects in the HPV-16/18 vaccine group (0.94 per 100 completed pregnancies)

- 28 subjects in the control groups (0.91 per 100 completed pregnancies)
- 1 subject did not receive any study vaccination.

There was no major difference in the reporting frequency of congenital anomalies in 100 completed pregnancies by country. The sponsor notes that approximately half of the congenital anomalies were reported in Study HPV-009 in Costa Rica. The majority of reports are derived from subjects participating in the large phase III clinical Studies HPV-008, HPV-009 and HPV-015.

Timing of exposure: From the 60 congenital anomalies reported, the mother's last menstrual period (LMP) was unknown in 7 cases, but the onset dates were greater than 12 months after the last vaccine dose in 6 cases and in one case the mother did not receive the vaccine. Of the 53 cases with reported Last Menstrual Period (LMP), the estimated date of conception (EDC) was calculated as the LMP + 14 days. This is based on the assumption that ovulation/conception occurs on cycle day 14 in the average 28 day menstrual cycle. Among these 53 cases, there were 6 reports of congenital anomalies in offspring of 5 study subjects (1 twin pregnancy) where exposure to study vaccine occurred within 15 days after the estimated date of conception. It is reported that exposures during the first 2 weeks after conception are not known to cause congenital anomalies in human embryos. For the remaining 47 reports, the study subjects were exposed to the study vaccine before the estimated date of conception, as follows:

- Within 30 days before the EDC: 2 reports
- Within 30 to 60 days before the EDC: 5 reports
- >61 days before the EDC: 40 reports

GSK provided summary tables of children born with congenital anomalies in women who received Cervarx and control material in studies reported in the BLA. In review of these tables, there was no specific anomaly identified in offspring of women whoc received Cervarix™ or control (ALU or Havrix). In addition, they also presented a summary of 6 reports of congenital anomalies in offspring of 5 study subjects (1 twin pregnancy) where exposure to study vaccine occurred 1-15 days after the estimated date of conception. Of these events, there were 4 reports in offspring of control recipients and 2 reports in offspring of HPV recipients. In the pooled control group, there was 1 child with anencephaly in the aluminum hydroxide group and one in the Havrix control group.

GSK convened a panel of three experts to review the congenital anomalies. The external experts concluded that there is **no evidence** that the risk of birth defects in children of women who were immunized with Cervarix™ prior to pregnancy is measurably increased or that any particular birth defect occurs in excess among these children. However, the experts further expressed the opinion that the data available to assess the potential reproductive toxicity of Cervarix™ are limited.

Neuroinflammatory and Musculoskeletal events: In the original BLA submission, CBER had noted a numerical imbalance in the number of events of potential neuroinflammatory etiology when comparing the HPV and control groups in studies submitted to the BLA to support licensure of Cervarix™. CBER also requested additional data for musculoskeletal events. Several steps were taken. Because the vaccine uses an adjuvant with MPL, CBER requested that GSK provide a meta-analysis to compare the rates of such events. The methodology was proposed by GSK and reviewed by the CBER statistician prior to proceeding with the meta-analysis. CBER suggested a listing of terms to use to search in the databases. In addition, CBER requested a consultation from a neurologist with expertise in neuroinflammatory events (as well as an internal consultation from a neurologist within FDA).

GSK provided meta-analyses for adverse events related to neuroinflammatory events and musculoskeletal events in HPV vaccines in all studies in IND -(b)(4)-. They also provided additional analyses for products which contained AS04 adjuvant (Level 2 analyses); analyses for products with any MPL-containing adjuvants (Level 3); and analyses of all products in preventive and therapeutic programs which have used MPL. The most pertinent analysis is the Level 1 analysis since it directly applies to HPV products adjuvanted with AS04. The different analyses are described here.

- **Level 1 analysis:** defined as the analyses of all IND and non-IND studies in the HPV vaccine program. These analyses were based on all serious adverse events (SAEs) and unsolicited adverse events, as well as on medically significant events (MsAEs) and new onset of chronic diseases (NOCDs), when available, reported in the HPV trials for events of interest. Studies included in Level 1 analyses were all studies conducted with the HPV-16/18 L1 VLP AS04 vaccine (BB-IND -(b)(4)-), with the --------(b)(4)---------- vaccine and with the ----------(b)(4)----------).
- **Level 2 analysis:** defined as the analyses of all IND and non-IND studies in the 3 major programs which have evaluated vaccines adjuvanted with AS04, i.e., all studies included in Level 2 analyses were all studies already included in Level 1 analyses, as well as the studies performed with the HSV AS04-adjuvanted vaccine (BB-IND -(b)(4)-), ----------(b)(4)-- vaccine and with the HBV AS04-adjuvanted vaccine (licensed in Europe under the name Fendrix™). These analyses were based on all SAEs and unsolicited adverse events, as well as on MsAEs and NOCDs (when available), reported in the HPV, HSV and HBV trials for events of interest.
- **Level 3 analysis:** defined as the analyses of IND and non-IND studies sponsored by GSK or external collaborators with all prophylactic programs which have evaluated vaccines with MPL-containing adjuvants, i.e., studies included in Level 3 analyses are all studies already included in Level 2 analyses, as well as the studies performed with other vaccines containing MPL, such as ----------(b)(4)----------, as well as other (smaller) vaccine programs using MPL-containing adjuvants. In addition to the adverse events specified for programs for programs included in the Level 1 and 2 analyses, Level 3 analyses include SAEs reported in these other prophylactic programs using MPL.
- **Level 4 analysis:** defined as the analyses of all IND and non-IND GSK and -(b)(4)- studies in all therapeutic vaccine programs, in cancer vaccine programs and studies conducted by -(b)(4) which have used MPL-containing adjuvants. These analyses were run independent from the Level 1, 2 and 3 analyses, since the profile of most subjects included in these programs differs significantly from the healthy subjects included in other vaccine programs. These analyses only included SAEs obtained from either safety databases or study publications.

In the meta-analysis, GSK considered two reporting periods for the start date of a reported neuroinflammatory or musculoskeletal event:

- throughout the entire follow-up up to the data lock-point of August 31, 2008 (except Study HPV-009: data lock-point of July 1, 2008) for levels 1 to 4,
- a 12 month follow-up period following first vaccination for levels 1 and 2 (a "theoretical risk" period covering the 6 month period of active vaccination during which the three doses of Cervarix™ are administered and the 6 month period following the end of the vaccination course, during which the active immune response to vaccination is expected to be high and autoimmune diseases that could potentially be causally associated with vaccination might be expected to start).

Rates of events were compared between treatment groups (MPL and non-MPL groups) with an adjustment for study effect to assess whether there was an increased risk for any of the events evaluated. The common relative risk across studies and its 95% CI was estimated on the exact conditional likelihood approach adjusted for the study effect. No relative risk was calculated for uncontrolled studies since this calculation requires a reference group.

The number of subjects considered for Level I analysis is presented in the table below.

Table 36 - Number of subjects included in Level I analysis

Level	Group	Initial meta-analysis DLP 6/30/07*	CR letter response DLP 12/31/07**	Updated meta-analysis DLP 8/31/08***
1	MPL group	24739	32413	34466
	Non-MPL group	19437	25438	27742
	Total	44176	57851	62208

DLP = data lock-point
* DLP of June 30, 2007 for all studies except for Study HPV-008 (July 31, 2007) and Study HPV-009 (March 21, 2007)
**DLP of December 31, 2007 for all studies except for Study HPV-009 (December 14, 2007)
*** DLP of August 31, 2008 for all studies except for Study HPV-009 (July 1, 2008).
Source: Table 59, p. 178, Supplemental safety update

Neuroinflammatory events: In the original BLA, there were 9 subjects who participated in GSK trials involving HPV vaccines adjuvanted with AS04 were reviewed. GSK convened an expert panel of neurologists and their diagnoses are denoted by "[ ]" in the table below. In addition to the cases included in the table below, there was one additional 27 year old female with report of transverse myelitis @ 22 months after dose 3 Cervarix™ [CIS].

Table 37 - Neuro-inflammatory Events which occurred in the HPV vaccine development programs

MPL			Non-MPL		
HPV studies					
Subject ID/Study	Event	Time to Event	Case ID	Event	Time to Event
704/Study 014	Optic neuritis [CIS]	9 days postdose 1	1658/010	Multiple sclerosis [not new case]	60 days postdose 1 Gardasil
1264/Study 014	Multiple sclerosis [CIS]	25 days postdose 2	11937/008	Optic neuritis [CIS]	134 days postdose 3
2030/study Tetra 051	Myelitis [Insufficient diagnosis]	47 days postdose 2	14111/008	Optic neuritis [CIS]	23 months postdose 3
0037/study 012	Demyelinating disease [CIS]	129 days postdose 2			
1020/study 008	Optic neuritis [CIS]	15 months postdose 3			
2475/008	Optic neuritis and multiple sclerosis [CIS]	17 months postdose 3			

[ ] = expert panel diagnosis

Concucrrently but independent from the GSK expert analysis, CBER requested a neurology consultation from an expert neurologist to conduct an analysis of these neuroinflammatory cases. In general, events that occurred within 3 months of vaccination were considered to occur within a time frame which was biologically plausible if a relationship was being considered. The expert concluded that the data was insufficient to establish a link, although it is sufficient to raise concern. Continued tracking of such events was recommended in the post-marketing period.

GSK performed a updates overall assessment of all neuroinflammatory events which occurred in clinical studies with GSK's MPL–containing products, up to the new data lockpoint of August 31, 2008 (except for Study HPV-009 for which the data lock-point is July 1, 2008). For the updated level 1 to 3 analyses, from the data lock-point for the response to the CR Letter (December 31, 2007; December 14, 2007 for Study HPV-009) up to the data lockpoint of August

31, 2008 (for all studies except Study HPV-009: July 1, 2008) there were six new events reported: four events in level 1 controlled studies, one event in level 1 uncontrolled studies and one event in level 2 controlled studies) and one event (optic neuritis) in level 1 controlled studies was changed by the investigator to multiple sclerosis in a follow-up report. In all new cases, the neuroinflammatory diseases occurred approximately 2 to 6 years after third study vaccination. These lengthy time intervals were not supportive of a relationship to vaccination. GSK also notes that in three of these cases (B0522773B, B0532741A, R0000296A), supportive and confirmatory paraclinical examinations were not described to corroborate diagnosis or exclude other possible diagnoses and therefore it was not possible to estimate diagnostic certainty.

Table 38 - Additional cases for levels 1 neuroinflammatory events in controlled and uncontrolled studies

Level (control)	MedDRA Verbatim Term	Adverse Event verbatim	Study	Subject	Treatment Allocation
1 (controlled)	Optic neuritis	Optic neuritis	HPV-008	15004	HPV 16/18 vaccine
1 (controlled)	Multiple sclerosis	Multiple sclerosis	HPV-008	1762	HPV 16/18 vaccine
1 (controlled)	Multiple sclerosis	Multiple sclerosis	HPV-008	73746	HPV 16/18 vaccine
1 (controlled)	Myelitis	Myelitis	HPV-023	7179	HPV 16/18 vaccine
1 (uncontrolled)	Optic neuritis	Retrobulbar pain*	HPV-048	2293	HPV 16/18 vaccine formulated with 40 mcg each VLP

*The subject did NOT have optic neuritis, but rather pain behind the eyes (retrobulbar pain) which resolved.
Source: STN 125259.48, Supplemental safety update, Table 64, p. 181

For the level 1 analysis of controlled HPV studies throughout the entire follow-up period, there were overall 10 subjects reporting at least one neuroinflammatory event with seven subjects in the MPL group and three subjects in the non-MPL group. One subject in the MPL group reported both optic neuritis and multiple sclerosis. There were 4 new cases added since the time of the original analysis. These included two subjects developed multiple sclerosis, one subject developed myelitis, and one subject developed optic neuritis. Considering all events, GSK calculated the overall relative risk for neuroinflammatory events in level 1 was calculated at 2.33 (95% CI: 0.53; 13.97). For multiple sclerosis, the relative risk was 1.50 (95% CI: 0.17, 17.97), and for optic neuritis, the relative risk was 3.00 (95% CI: 0.24, 157.50). With one case of myelitis and 1 case of transverse myelitis in the MPL group, the relative risk was calculated as INF. (It is noted that there was question as to the diagnosis of the first case of myelitis by all neurologists who reviewed the case, and the other case of transverse myelitis occurred 22 months after the last vaccination, making relationship to vaccination unlikely.

For the level 1 analysis of controlled HPV studies during the 12 month follow-up period following dose 1, there were overall 2 subjects reporting at least one neuroinflammatory event with both events in the Non-MPL group (1 case optic neuritis and 1 case multiple sclerosis).

For the level 1 analysis of uncontrolled HPV studies throughout the entire follow-up period, there was one additional event which was reported as optic neuritis which occurred at 3 days after dose 1 of an HPV vaccine formulated with a higher dose of each antigen (40 mcg) as compared to Cervarix™. However, from the history provided, the subject complained of retrobulbar pain and not optic neuritis, so the event was coded incorrectly. The subject went onto receive the 2nd and 3rd doses of the vaccine without problem. Therefore, there were a total of five neuroinflammatory events: one case of multiple sclerosis, two cases of optic neuritis, one case of myelitis and one case of demyelination disease. Therefore, throughout the entire study period, in 6951 subjects who received an HPV vaccine adjuvanted with MPL, 5/6951 (0.07% [95% CI: 0.02, 0.17%])

subjects had at least one symptom; 1/6951 (0.01% [95% CI: 0.00, 0.08%]) had demyelinating disease; 1/6951 (0.01% [95% CI: 0.00, 0.08%]) had multiple sclerosis; 1/6951 (0.01% [95% CI: 0.00, 0.08%]) had myelitis; and 26951 (0.03% [95% CI: 0.00, 0.10%]) had optic neuritis.

The GSK neurology panel concluded that based on their review of data up to the data lock-point of December 31, 2007 that there was not an increased risk of neuroinflammatory disorders following vaccination with MPL-containing vaccines.

In a post-marketing study, CBER has requested that events of potential autoimmune nature, including neuroinflammtory events, be followed and reported.

Grave's disease: In review of the original BLA, CBER suggested repeating analysis of Grave's disease to ensure there was no statistical difference in rates between non-MPL material recipients and MPL-containing study material.

GSK provided this update, and there were no imbalances statistically when comparing the occurrence rates of Graves disease between the MPL group and non-MPL group for all three levels analysed. There were no reports of Graves disease in level 4. No significant imbalances in the occurrence rates of Graves disease between the MPL group and non-MPL group were observed in individual studies.

Musculoskeletal events: In the original BLA, one comment pertained to events of potential musculoskeletal nature and request for additional information on such events.

In response, GSK performed an overall assessment of all musculoskeletal events which occurred in clinical studies with GSK's MPL–containing products, up to the new data lock-point of August 31, 2008 (except for Study HPV-009 for which the data lock-point is July 1, 2008).

Level 1 analysis: For the level 1 analysis of controlled HPV studies, **throughout the entire follow-up period**, there were overall 68 subjects reporting at least one musculoskeletal event.

With 39 subjects in the MPL group and 29 subjects in the non-MPL group, the overall relative risk was 1.31 (95% CI 0.79; 2.20). The most frequently reported musculoskeletal events were:

- arthritis with 9 events in the MPL group and 11 events in the non-MPL group (RR =0.82, 95% CI 0.30; 2.17),
- fibromyalgia with 10 events in the MPL group and 6 events in the non-MPL group (RR = 1.66, 95% CI 0.55; 5.57),
- rheumatoid arthritis with 10 events in the MPL group and 8 events in the non-MPL group (RR = 1.25, 95% CI 0.44; 3.65),
- systemic lupus erythematosus with 4 events in the MPL group and 2 in the non-MPL group (RR = 2.00, 95% CI 0.29; 22.14).
- For juvenile rheumatoid arthritis, reactive arthritis and scleroderma, there were one, four and one events respectively in the MPL group and 0 in the non-MPL group.
- Arthropathy was reported infrequently with one event in the MPL group versus two events in the non-MPL group (RR = 0.50, 95% CI 0.01; 9.55).

For the level 1 analysis of controlled HPV studies, during the **12 month follow-up period following dose 1**, there were overall 31 subjects reporting at least one musculoskeletal event with 19 events in the MPL and 12 events in the non-MPL group (RR = 1.58, 95% CI 0.73; 3.57).

For this reporting period, the most frequently reported musculoskeletal events were arthritis, fibromyalgia and rheumatoid arthritis with similar number of events for arthritis, and fibromyalgia in the MPL and non-MPL groups but a higher number of rheumatoid arthritis events were reported in the MPL group than in the non-MPL group, although the lower limit of the confidence interval remained below 1:

- arthritis with seven events in the MPL group and six events in the non-MPL group (RR = 1.16, 95% CI 0.33; 4.19),
- fibromyalgia with five events in the MPL group and four events in the non-MPL group (RR = 1.25, 95% CI 0.27; 6.29),
- rheumatoid arthritis with six events in the MPL group and one event in the non-MPL group (RR = 6.02, 95% CI 0.73; 276.71),
- For reactive arthritis, there were two events in the MPL group and for arthropathy, there was one event reported in the non-MPL group.

The GSK analysis is presented below.

Table 39 - Percentage of subjects reporting the occurrence of musculoskeletal events reported between dose 1 and 6 months after dose 3, classified by CBER Verbatim Terms with estimated relative risks and homogeneity test (Level 1 [controlled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL Group N=27515	Non-MPL Group N=27742	Relative Risk (MPL over non-MPL) 95% CI	p-value homogeneity
At least one symptom	19 (0.07%)	12 (0.04%)	1.58 (0.73,3.57)	0.1580
Arthritis	7 (0.03%)	6 (0.02%)	1.16 (0.33,4.19)	0.3758
Arthropathy	0 (0.0%)	1 (0.004%)	0.00 (0.00, 39.0)	NA
Fibromyalgia	5 (0.02%)	4 (0.01%)	1.25 (0.27, 6.29)	0.1780
Reactive arthritis	2 (0.007%)	0 (0.0%)	INF (0.19, INF)	NA
Rheumatoid arthritis	6 (0.02%)	1 (0.004%)	6.02 (0.73, 276.71)	0.8314

At least one symptom = at least one symptom experienced (regardless of the CBER Verbatim Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
INF=infinity, no cases are reported in the Non-MPL group
NA = Not applicable (p-value for homogeneity test is calculated when there is at least 1 case in each group and when the cases are reported in more than one study)
STN 125259.48, Supplemental safety update, Table 78, p. 200

For the level 1 analysis of **uncontrolled HPV studies, throughout the entire follow-up period,** of the 6951 subjects who received an HPV vaccine with MPL, there were a total of 14 subjects (0.30% [95% CI: 0.11, 0.34]) for which a musculoskeletal event was reported. Of these 14, 8/6951 (0.12% [95% CI: 0.05, 0.23)]) reported arthritis; 3/6951 (0.04% [95% CI: 0.01, 0.13]) reported arthropathy; 3/6951 (0.04% [95% CI: 0.01, 0.13]) reported reactive arthritis; and 2/6951 (0.03% [95% CI: 0.00, 0.10]) reported RA.

For the level 1 analysis of uncontrolled HPV studies, of the 6951 subjects who received HPV vaccine with MPL, during the 12 month follow-up period following dose 1, there were a total of 12 subjects (0.17% [95% CI: 0.09, 0.30]) for which a musculoskeletal event was reported, similar to the reporting of events throughout the entire follow-up period. Of these 12, 8/6951 (0.12% [95% CI: 0.05, 0.23)]) reported arthritis; 2/6951 (0.03% [95% CI: 0.00, 0.10]) reported arthropathy; and 3/6951 (0.04% [95% CI: 0.01, 0.13]) reported reactive arthritis.

Expert panel musculoskeletal events: GSK convened a panel of three experts to review of potentially autoimmune musculoskeletal events. The external expert panel reviewed 146 musculoskeletal events that were reported in 142 subjects up to the data lock-point of December

31, 2007 (except for Study HPV- 009: data lock-point of December 14, 2007) for all studies (controlled and uncontrolled) in levels 1 to 4 of analysis. Sixty-seven events reported in 65 subjects were not considered to be immune-mediated rheumatologic events and were mainly with degenerative or traumatic disorders or fibromyalgia. Of the remaining 79 events reported in 77 subjects, the classification as an immune-mediated rheumatologic event was uncertain for 43 events reported in 42 subjects because the case documentation was insufficient to permit adequate assessment to confirm or exclude an immune-mediated rheumatologic event. In the remaining 36 events, reported in 35 subjects, the case documentation was adequate to permit a classification as a confirmed immune-mediated rheumatologic event. In these totals are included events which occurred in **all** studies in which an HPV vaccine adjuvanted with MPL was administered. (These totals include studies HPV-009, HPV-010, and HPV-015, which have not been completed and final study reports not yet submitted for review, although it was thought to be important to ascertain as completely as possible the occurrence of these events in HPV vaccines administered to date).

For the level 1 analysis of confirmed immune-mediated rheumatologic events, throughout the entire follow-up period, there were overall 21 subjects reporting at least one event with 13 subjects in the MPL group and 8 subjects in the non-MPL group; the overall relative risk was 1.63 (95% CI 0.65; 4.14). The most frequently reported events were:

- arthritis with one event in the MPL group and four events in the non-MPL group (RR = 0.25, 95% CI 0.01; 2.53),
- rheumatoid arthritis with five events in the MPL group and three events in the non- MPL group (RR = 1.81, 95% CI 0.37; 9.66),
- systemic lupus erythematosus with three events in the MPL group and one event in the non-MPL group (RR = 2.39, 95% CI 0.25; 30.86).
- For juvenile arthritis and reactive arthritis, there were two events in the MPL group.

For the level 1 analysis of uncertain immune-mediated rheumatologic events, throughout the entire follow-up period, there were overall 5 subjects reporting at least one event with 3 subjects in the MPL group and 2 subjects in the non-MPL group; the overall relative risk was 1.88 (95% CI 0.21; 23.88). The most frequently reported events was:

- arthritis with three events in the MPL group and one event in the non-MPL group (RR = 3.00, 95% CI 0.24; 157.27).
- For rheumatoid arthritis, there was one event in the non-MPL group.

For the level 1 analysis of confirmed and uncertain immune-mediated rheumatologic events combined, throughout the entire follow-up period, there were overall 26 subjects reporting at least one event with 16 subjects in the MPL group and 10 subjects in the non-MPL group; the overall relative risk was 1.67 (95% CI 0.73; 3.87). The most frequently reported events were:

- arthritis with four events in the MPL group and five events in the non-MPL group (RR = 0.80, 95% CI 0.16; 3.71)
- rheumatoid arthritis with five events in the MPL group and four events in the non-MPL group (RR = 1.54, 95% CI 0.34; 7.08),
- systemic lupus erythematosus with three events in the MPL group and one event in the non-MPL group (RR = 2.39, 95% CI 0.25; 30.86),
- For juvenile arthritis and reactive arthritis, there were two events in the MPL group.

Table 40 - Percentage of subjects reporting the occurrence of immune-mediated rheumatologic events (confirmed and uncertain diagnosis combined) throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks (Level 1 [controlled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL Group N=25580	Non-MPL Group N=25438	Relative Risk (MPL over non-MPL) 95% CI
At least one symptom	16 (0.06%)	10 (0.04%)	1.67 (0.73, 3.87)
Arthritis	4 (0.02%)	5 (0.02%)	0.80 (0.16, 3.71)
Arhritis reactive	2 (0.01%)	0 (0.0%)	INF (0.19, INF)
Juvenile arthritis	2 (0.01%)	0 (0.0%)	INF (0.21, INF)
Rheumatoid arthritis	5 (0.02%)	4 (0.02%)	1.54 (0.34, 7.08)
Systemic lupus erythematosus	3 (0.1%)	1 (0.004%)	2.39 (0.25, 30.86)

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (
STN 125259.48, Supplemental safety update, Table 92, p. 212

GSK reported that the panel of experts recommended a second analysis be performed based on a search of MedDRA Preferred Terms in the CBER category of musculoskeletal events which was extended to other terms from other CBER categories of diseases as the experts considered these additional terms as relevant for an analysis of musculoskeletal disorders (extended musculoskeletal analysis). Additional terms were used to search the safety databases. Although additional subjects and events were captured (as compared to the analysis above), none of the relative risks reached statistical significance.

Table 41 - Percentage of subjects reporting the occurrence of musculoskeletal events (extended musculoskeletal analysis) throughout the entire follow-up period, classified by CBER Verbatim Terms with estimated relative risks and homogeneity test (Level 1 [controlled HPV studies] Total vaccinated cohort)

CBER Verbatim Term	MPL Group N=27515	Non-MPL Group N=27742	Relative Risk (MPL over non-MPL) 95% CI	p-value homogeneity
At least one symptom	41[+2] (0.1%)	38[+9] (0.1%)	1.08 (0.68, 1.72)	0.4847
Arthritis	9 (0.03%)	11 (0.04%)	0.82 (0.30, 2.17)	0.5051
Arthropathy	1 (0.004%)	2 (0.007%)	0.50 (0.01, 9.55)	0.2227
Cutaneous lupus	0 (0.0%)	1 (0.004%)	0.00 (0.0, 39.03)	NA
Dermatomyositis	0	1 (0.004)	0.00 (0.0, 39.03)	NA
Fibromyalgia	10 (0.04%)	6 (0.02%)	1.66 (0.55, 5.57)	0.1707
JRA	1 (0.004%)	0 (0.0%)	INF (0.03, INF)	NA
Psoriatic arthropathy	0 (0.0%)	2 (0.007%)	0.00 (0.0, 5.33)	NA
Raynaud's phenomenon	0 (0.0%)	3 (0.0.1%)	0.0 (0.0, 2.42)	NA
Reactive arthritis	4 (0.01%)	0 (0.0%)	INF (0.66, INF)	NA
Rheumatoid arthritis	10 (0.04%)	8 (0.03%)	1.25 (0.44, 3.65)	0.5701
Scleroderma	1 (0.004%)	0 (0.0%)	INF (0.03,INF)	NA
SLE	4 (0.01%)	2 (0.007%)	2.00 (0.29, 22.14)	0.2204
Vasculitis	2 (0.007%)	3 (0.01%)	0.67 (0.06, 5.82)	0.1715

At least one symptom = at least one symptom experienced (regardless of the CBER Verbatim Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
INF=infinity, no cases are reported in the Non-MPL group
NA = Not applicable (p-value for homogeneity test is calculated when there is at least 1 case in each group and when the cases are reported in more than one study)
Events highlighted in yellow were added in extended analysis as compared to initial analysis
Source: STN 125259.48, Supplemental safety update, Table 87, p. 217

For the level 1 analysis of uncontrolled HPV studies, throughout the entire follow-up period, there was no change in number of subjects (14) or breakdown identified, nor for the 12 month follow-up period, in which 12 subjects for which an event was reported.

In the Cervarix™ BLA and BLA resubmission, CBER reviewed the number of events and time to onset for events assess as of confirmed autoimmune etiology, those of unconfirmed autoimmune etiology, and those definitely not of autoimmune etiology. In review of the summary tables provided by GSK, several subjects were noted to be in the older age group. For example, in the subjects in the MPL group who developed a confirmed immune-mediated event, 3 of the subjects were noted to be 35-50 years of age; 2 of the subjects with juvenile arthritis had a prior history of juvenile arthritis; and one subject with SLE (included in deaths due to immunosuppression for treatment of an immune-mediated event) had blood from prior to vaccination which was positive for markers consistent with SLE. The day ranges from last vaccination to time to event for RA ranged from 76 days postdose 2 to 548 days postdose 3. Of the subjects in the non-MPL group who developed RA during the trials, the time to onset from last vaccination ranged from 56 days postdose 3 to 1145 days postdose 3. In review of those with uncertain diagnoses, several subjects in the MPL group developed single joint arthritis @ 1-112 days after receipt of dose 1-3. In some of these subjects, there were histories of prior injuries to the joints which may have contributed to the events. Fibromyalgia was included in the illnesses considered definitely not related to immune mediated illnesses. The etiology of this illness is not known.

Discussion of musculoskeletal events of potential autoimmune etiology: Siegrist et al[8] has recently assessed the incidence rates of diseases of potential autoimmune etiology in a large Health Maintenace Organization (HMO) in young women prior to the introduction of Gardasil into the recommended immunization schedule. In this cohort study in 2005, immune-mediated conditions were a frequent cause (10.3%) of emergency room consultation by adolescent girls. These events commonly occur in younger women as demonstrated in this one study (prior to the introduction of the Merck HPV product), and makes distinction between HPV vaccine related adverse reactions and events only observed by chance in temporal association difficult. The use of population-based data allows for identification of issues of potential concern and may help define illnesses that have occurred prior to the use of the vaccine, as well as using subjects as their own controls (pre- and post-vaccination), which may be helpful in distinguishing whether events are related or not related to vaccination.

Post-Marketing Studies:
GSK had initially proposed a large post-marketing study which was to be conducted in Scotland. The study was not able to be initiated, and CBER and GSK are in negotiations regarding a post-marketing study to be conducted in the United States. The proposed study (negotiations in progress) includes 44,000 females 10-25 years of age who receive Cervarix™. These subjects will be studied in an HMO setting. Subjects will optimally have been members of the HMO(s) for a year prior to entry into this post-marketing study so as to collect adequate pre-vaccination background data. The control group will include women matched for age and geographic location, and the control group may also include those who are receiving another vaccine, (perhaps Menactra). The primary objective will be to collect all diseases of potential autoimmune etiology, and a secondary objective will be to institute an enhanced pregnancy registry. The final list of autoimmune illnesses will be specified with finalization of the protocol.

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[8] Siegrist C et al. HPV immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. Pediatric Infectious Disease Journal 2007; 26:979-984.

For Post Marketing Safety Update Reporting, CBER will request that all safety reports be submitted within 15 days.

As noted, the specifics of the protocol have not been finalized, and further information is expcted to be available at the time of the VRBPAC meeting.

SUMMARY STATEMENTS

Overall Efficacy

- Based on the available data, Cervarix™ has been demonstrated to be effective in preventing genital dysplasias (CIN2+ and CIN1) associated with HPV 16 and/or 18 in 15-25 year old women who are naïve for the relevant vaccine HPV types.
- Cervarix™ is not effective in preventing genital dysplasias (CIN2+ and CIN1) related to vaccine HPV types for which the subject has been exposed.
- Cervarix™ may have an impact on reducing gental dysplasias (CIN2+) related to HPV-31, but analyses involving multiple HPV types (both vaccine and non-vaccine) are complicated.

Overall Immunogenicity

- Cervarix™ is immunogenic and has been demonstrated to elicit anti-HPV 16 IgG and HPV-18 IgG as measured by ELISA. From studies HPV-001/007, the duration of immune response is at least 76 months. Antibody levels peak after dose 3 at Month 7, and decrease to a level at Month 18-24 which appears to plateau out to Month 76 (longest time point reported). From study HPV-008, antibody responses elicited to anti-HPV 16 and anti-HPV-18 as measured by neutralizing assays appear to follow a similar pattern out to Month 24.
- IgG antibodies to anti-HPV-31 and HPV-45 as measured by ELISA have been demonstrated in a subset of subjects, with a high rate of seroresponse. However, anti-HPV 31 and anti-HPV 45 antibodies as measured by neutralizing assays are elicited in a smaller percentage of subjects, and do not appear to be long-lasting.
- Cervarix™ is immunogenic in young females 10-14 years of age (in whom genital testing is not possible), and immune responses in this age group are higher in regards to GMTs elicited when anti-HPV 16 and anti-HPV 18 are measured by ELISA. Immunobridging to females 10-14 years of age has been conducted from subjects 15-25 years of age who participated in study HPV-001, as well as from subjects 15-25 years of age who participated in study HPV-012.
- Lot-to-lot consistency has been demonstrated for Cervarix™ manufactured by different processes, as well as for different lot productions.
- Given the very high effectiveness of Cervarix™ in prevention of CIN2+ related to HPV 16 and/or 18, very few breakthrough cases have occurred, and it was not possible to identify an immune correlate of protection.

Overall Safety

- In general, Cervarix™ elicits solicited adverse events (pain, swelling, redness) and specific solicited general adverse events to a lesser degree (including myalgia and arthralgia) in the 7 days after vaccination when considered overall/subject. The incidences of these solicited adverse events are higher when compared to subjects who received the active control Havrix. However, the compliance rates of completion of the study were high in both treatment groups were high across studies.
- Regarding Deaths which occurred in the studies, the number and proportions of events were similar in both treatment groups.
- Regarding Serious Adverse Events, the proportions of subjects in individual controlled studies reviewed as well as across all studies presented overall were generally comparable in the Cervarix™ and control groups.

- Regarding New Onset Chronic Diseases and New Onset Autoimmune Diseases identified in the controlled studies, there was no identified imbalance in the proportions of subjects with such events. Events related to potential autoimmune etiology will be assessed in post-marketing studies.
- In the original BLA review, there was a numerical imbalance in events of potential neuroinflammatory nature. Expert opinions provided to CBER and to GSK, as well as extensive meta-analyses of such events across HPV studies (as well as studies containing AS04 and MPL) have not demonstrated statistically significant relative risks for such events. Nonetheless, such events will be collected in a planned post-marketing observational study (specific protocol under negotiation).
- In the original BLA review, CBER requested additional information regarding events of musculoskeletal nature of potential autoimmune etiology. GSK convened an expert panel and provided a meta-analysis of these events as well. Relative risks for these events did not reach statistical significance. Nonetheless, such events will be collected in a planned post-marketing observational study which is being negotiated.
- An imbalance in the proportion of subjects who experienced a spontaneous abortion was noted in subjects who had received Cervarix™ in the time period around estimated date of conception, but not in pregnancies overall. Possible confounding factors include a possible under-reporting of elective abortions in countries in which abortions are not approved (this is difficult to ascertain). Because of this imbalance, an enhanced pregnancy registry will be instituted to follow pregnancies in women who receive Cervarix™ inadvertently during pregnancy.

ATTACHMENTS

Attachment #1 is Cervarix New Onset Chronic Disease Methodology

Methodology to Identify New Onset Chronic Diseases (NOCD)

Disease/Disorder		MedDRA Level	MedDRA Code
Autoimmune disorders		HGLT	10003816
Blood autoimmune disorder		HLT	10003817
	Anaemia haemolytic autoimmune	PT	10002046
	Antiphospholipid syndrome	PT	10002817
	Cold type haemolytic anaemia	PT	10009868
	Coombs positive haemolytic anaemia	PT	10010941
	Idiopathic thrombocytopenic purpura	PT	10021245
	Pernicious anaemia	PT	10034695
	Warm type haemolytic anaemia	PT	10047822
	Autoimmune thrombocytopenia	PT	10050245
	Evan's syndrome	PT	10053873
	Autoimmune neutropenia	PT	10055128
Endocrine autoimmune disorder		HLT	10003818
	Basedow's disease	PT	10004161
	Insulin autoimmune syndrome	PT	10022472
	Polyglandular autoimmune syndrome type I	PT	10036072
	Polyglandular autoimmune syndrome type II	PT	10036073
	Autoimmune thyroiditis	PT	10049046
	Diabetic mastopathy	PT	10059134
	Lymphocytic hypophysitis	PT	10063685
	Polyglandular autoimmune syndrome type III	PT	10064115
Hepatic autoimmune disorder		HLT	10003820
	Autoimmune hepatitis	PT	10003827
	Biliary cirrhosis primary	PT	10004661
Muscular autoimmune disorder		HLT	10003821
	Myasthenia gravis	PT	10028417
	Myasthenia gravis neonatal	PT	10028419
	Polymyalgia	PT	10036097
	Polymyalgia rheumatica	PT	10036099
	Polymyositis	PT	10036102
	Ocular myasthenia	PT	10049168
	Myasthenia gravis crisis	PT	10062758
Lupus erythematosus and associated conditions		HLT	10025136
	Lupoid hepatic cirrhosis	PT	10025129
	Lupus encephalitis	PT	10025130
	Lupus nephritis	PT	10025140
	SLE arthritis	PT	10040968
	Systemic lupus erythematosus	PT	10042945
	Systemic lupus erythematosus rash	PT	10042946
	Lupus-like syndrome	PT	10050551
	Cutaneous lupus erythematosus	PT	10056509
	Lupus pneumonitis	PT	10057481
	Neonatal lupus erythematosus	PT	10057887
	Lupus vasculitis	PT	10058143
	Pericarditis lupus	PT	10058149
	Lupus endocarditis	PT	10058225
	Peritonitis lupus	PT	10062898
	Neuropsychiatric lupus	PT	10063663
Autoimmune disorders NEC		HLT	10003816
	Ankylosis spondylitis	PT	10002556
	Cryoglobulinaemia	PT	10011474

Disease/Disorder		MedDRA Level	MedDRA Code
	Gastritis atrophic	PT	10017860
	Goodpasture's syndrome	PT	10018620
	Keratoconjunctivitis sicca	PT	10023350
	Keratoderma blenorrhagica	PT	10023358
	Mixed connective tissue disease	PT	10027754
	Reiter's syndrome	PT	10038294
	Sicca syndrome	PT	10040633
	Sjogren's syndrome	PT	10040767
	Sympathetic opthalmia	PT	10042742
	Leukoencephalomyelitis	PT	10048999
	Toxic oil syndrome	PT	10051222
	Cryofibrinogenaemia	PT	10051229
	Encephalitis allergic	PT	10056387
	Nephritis autoimmune	PT	10058948
	Acute haemorrhagic leukoencephalitis	PT	10058994
	Autoimmune disorder	PT	10061664
Rheumatoid arthritis and associated conditions		HLT	10021428
	Felty's syndrome	PT	10016386
	Rheumatoid arthritis	PT	10039073
	Rheumatoid lung	PT	10039081
	Rheumatoid vasculitis	PT	10048628
	Rheumatoid nodule	PT	10048694
	Juvenile arthritis	PT	10059177
	Laryngeal rheumatoid arthritis	PT	10059669
Scleroderma and associated disorders		HLT	10039711
	CREST syndrome	PT	10011380
	Morphoea	PT	10027982
	Scleroderma	PT	10039710
	Systemic sclerosis	PT	10042953
	Systemic sclerosis pulmonary	PT	10042954
	Scleroderma renal crisis	PT	10062553
Skin autommune disorders NEC		HLT	10052738
	Benign familial pemphigus	PT	10004265
	Dermatitis herpetiformis	PT	10012468
	Dermatomyositis	PT	10012503
	Eosinophilic fasciitis	PT	10014954
	Herpes gestationis	PT	10019939
	Linear IgA disease	PT	10024515
	Pemphigoid	PT	10034277
	Pemphigus	PT	10034280
	Vitiligo	PT	10047642
Acute and chronic thyroiditis		HLT	10043779
	Thyroiditis	PT	10043778
	Thyroiditis acute	PT	10043780
	Thyroiditis chronic	PT	10043781
	Thyroiditis subacute	PT	10043784
	Autoimmune thyroiditis	PT	10049046
Optic neuritis	Optic neuritis	PT	10030942
	Optic neuritis retrobulbar	PT	10030945
	Vision blurred	PT	10047513
	Blindness	PT	10005169
	Visual acuity reduced	PT	10047531
	Visual evoked potential abnormaly	PT	10047549

Disease/Disorder		MedDRA Level	MedDRA Code
Multiple sclerosis	Multiple sclerosis Demyelineting disorder Gait disturbances Muscle weakness Paresthesias (Cognitive impairment) (Nuclear magnetic resonance imaging brain abnormal)	PT HLGT HLT LLT PT LLT PT	10028245 10012303 10017578 10028350 10033775 10009846 10029818
Transverse myelitis	Myelitis Transverse Muscle weakness Low back pain Paraesthesias and dysaesthesias Paralysis (Urinary retention) (Neurogenic bladder)	PT LLT LLT HLT PT PT PT	10028527 10028350 10024891 10033788 10033799 10046555 10029279
Guillain-Barre syndrome	Guillain-Barre syndrome Muscle weakness Paraesthesias and dysaesthesias	PT LLT HLT	10018767 10028350 10033788
Diabetes mellitus insulin-dependent	Diabetes mellitus Diabetes mellitus (incl. subtypes) Glucose metabolism disorders (incl. diabetes mellitus)	PT HLT HLGT	10012601 10012602 10018424
Uveitis	Uveitis Eye pain Eye redness Photophobia	PT PT LLT PT	10046851 10015958 10015963 10034960
Glomerulonephritis	Lupus nephritis Proteinuria Haematuria Glomerular filtration rate decreased (Hypoproteinemia) (Oedema) Blood urea increased Blood creatinine increase	PT PT PT PT PT PT PT PT	10025140 10037032 10018867 10018358 10021083 10030095 10005851 10005483
Hepatitis	*already identified as "hepatitis autoimmune" above*	PT	
Inflammatory bowel disease	Inflammatory bowel disease	PT	10021972
Crohn's disease	Crohn's disease	PT	10011401
Ulcerative colitis	Ulcerative colitis Rectal bleeding	PT LLT	10009900 10038035
Coeliac disease	Coeliac disease	PT	10009839
Sarcoidosis	Sarcoidosis Angiotensin converting enzyme increased	PT PT	10039486 10049530
Asthma	Asthma	PT	10003553
Allergies	Immune system disorders Allergic conditions	SOC HLGT	 10001708
Auto immunity analyses		HLT	10003828

HLGT = High Level Group Term (for analysis purposes, includes all Preferred Terms under this category)
HLT = High Level Term (for analysis purposes, includes all Preferred Terms under this category)
LLT = Low Level Term (for analysis purposes, includes all Preferred Terms under this category)
PT = Preferred Term;
SOC = System Organ Class
Source: STN 125259.48, CSR 007, Month 36, Supplement 196, p. 446-448

Attachment #2 Synopses of the clinical phase I, IIa, clinical studies

HPV-002: Safety and immunogenicity of HPV 16/18 and components (N=49, 18-30 yrs)

- **Summary results:** The HPV-16, HPV-18 and HPV-16/18 VLP vaccines used in this study were tolerated and no limiting toxicities were observed. Serologica1 and cell mediated immune responses to both HPV-16 Ll VLPs and HPV-18 Ll VLPs, separately and in combination, were detected after two injections of study vaccine. There was no evidence of interference between the HPV-16 and HPV-18 components of the HPV-16/18 VLP vaccine

with respect to stimulation of an immune response to each of these components. Boosting of the serological immune response to HPV-16 L1 VLP vaccine was observed in all subjects after dose 3 of this vaccine. An annex report was provided as well for a small number of subjects who were followed out to 4.5 years after dose 1. At 4.5 years after the first injection, ELISA binding antibody responses to HPV-16 persisted in all subjects, and inhibitory ELISA responses to HPV-16 were detectable in 1/3 (33.3%) subject. In the sponsor's exploratory analyses of HPV-16 and HPV-18 lymphoproliferative responses and specific Interferon-gamma (IFN-γ) responses, these levels remained elevated in the 7 subjects from 2 to up to 4.5 years.

HPV-003: Safety and immunogenicity in previously infected women (N=31 C, 30 AlOH3; 18-30 yrs)

- **Summary Results:** In women previously infected with HPV 16 and/or HPV 18, the HPV 16/18 vaccine and the aluminum hydroxide control were tolerated and did not elicit a safety signal. Immunization was not associated with enhanced rates of clearance of HPV-16 or HPV-18 viral DNA as detected by the ----------(b)(4)----------. Antigen- specific antibody responses to both HPV-16 and HPV-18 were demonstrated after two injections of study vaccine and were boosted after a third injection. In an annex report to study 003, testing for clearance was conducted with another assay, the --------(b)(4)--------- PCR assay, and there was again no evidence of enhanced clearance of HPV 16 and/or 18 in vaccine recipients.

HPV-004: Safety and immunogenicity of HPV 16/18 with AS04, aluminum hydroxide, or non-adjuvanted (N=60, 18-30 yrs)

- **Summary Results:** 40 mcg HPV 16/18 vaccine formulated with AS04, aluminum hydroxide or no adjuvant did not elicit a specific safety signal. Antigen-specific humoral and cellular immune responses to both HPV-16 and HPV-18 were demonstrated after two injections of study vaccine, were boosted after a third injection, and remained elevated above baseline at Study Day 360. ELISA titers were higher in the AS04 group than in the aluminum hydroxide or no-adjuvant groups at Study Day 210. The kinetic profile of antibody to HPV-16 and HPV-18 was similar to the profile of neutralizing antibody, including a trend to highest responses to HPV-16 in the AS04 group. Although the AS04 formulation was noted to be slightly more reactogenic, it appeared to induce the greatest humoral responses. In review of the results, the anti-HPV 16 and anti-HPV 18 antibody levels as measured by ELISA were higher in the AS04 adjuvanted group > aluminum hydroxide group > no-adjuvant group. A higher immune response was postulated to possibly be associated with a prolonged duration of prevention of HPV 16 and/or 18 related disease, although this would not be able to be proven unless there is evidence of actual prolonged prevention. Regarding the parameters for cell-mediated immunity (lymphproliferative response, and IFN-γ and IL-5 release), the response to HPV 16/18 vaccine in these exploratory analyses were similar in the AS04 and aluminum hydroxide-adjuvanted product. It is noted that both adjuvanted products elicited higher immune reponses (humoral and cell mediated immune response) as compared to the non-adjuvanted product. The Applicant used these data to support going further in development of the candidate vaccine using the AS04 adjuvant. Although no specific safety signal was identified (except for more local reactogenicity, i.e., pain with the AS04 adjuvanted product), a much larger safety database would be needed to assess for more rare adverse events.) Annex reports were also provided in which measures of cell mediated immunity were measured out to 2 years and antibodies by ELISA out to 4 years.

HPV-005: Safety and immunogenicity of HPV 16/18 at 3 doses of VLPs with either aluminum hydroxide or AS04 (6/6+AS04, 20/20+AS04, 60/60+AS04, 20/20+AlOH3) (N=209, 18-30 yrs)

- **Summary Results:** HPV 16/18 formulations, 12 mcg with AS04, 40 mcg with AS04, 120 mcg with AS04, and 40 mcg with aluminum hydroxide were generally well tolerated. There were no apparent dosage effects seen in the frequency, duration, or intensity of solicited AEs or the frequency of unsolicited AEs in the AS04 groups except for injection site swelling which was seen more frequently in the 120 mcg dose group. Local reactions at the injection site were more frequent for all AS04 formulations compared to the aluminum hydroxide formulation, but there was no apparent difference in systemic AEs. Serological and cell-mediated immune (CMI) responses to both HPV 16 and HPV 18 were demonstrated after 2 injections of study vaccine (one each on study days 0 and 30), were boosted by dose 3 administered at study day 180, and remained elevated at study day 360. Although there was no consistent or clear evidence of a dosage effect on cellular responses demonstrated for the AS04 formulations, there was a trend towards higher ELISA titers with increasing dose level that suggested that the 12 mcg AS04 formulation was less immunogenic than the other AS04 doses tested. The sponsor used the higher ELISA titers as support for selection of HPV 16/18 40 mcg with AS04 formulation for subsequent clinical development. In annex reports, after immunization of volunteers with 3 doses of the AS04 and aluminum hydroxide-adjuvanted HPV-16/18 vaccines, HPV-16/18 IgG-specific responses in Cervico-vaginal secretions (CVS) were found in the majority, if not all, immunized volunteers. At Study Day 210, IgG HPV-16/18-specific responses in the serum and CVS were detected in 80%—90% of volunteers who received the candidate 40-µg dose of the AS04-adjuvanted HPV-16/18 vaccine. There appeared to be a dose effect on the magnitude of the responses found in the CVS and serum in the SBAS4 12-µg, 40-µg, and 120-µg treatment groups. In addition, the presence and level of serum and CVS antibody levels seemed to be highly correlated. In review of the data up to 360 days after dose 1, anti-HPV 16 and HPV-18 antibodies measured in cervical secretions were equivalent or slightly higher with the aluminum hydroxide adjuvanted product as compared to the 40 mcg AS04 formulation (albeit in a small number of subjects). There was a positive correlation between serum anti-HPV 16 and HPV-18 antibodies with antibodies in cervical secretions.
- In another annex report for study HPV-005 with follow-up out to 4 years after receipt of dose 1, the sponsor reported that in both the AS04 and aluminum hydroxide groups, antibody levels increased through Study Day 60, peaked at Study Day 210, and had declined less than one log10 through Study Year 2. Less pronounced decline in antibody levels, up to 3-fold, occurred from Study Year 2 through Study Year 4, except for HPV-16 in the aluminum hydroxide group for which antibody levels remained steady. These values were well above the pre-vaccination titers. For all 4 years of the study, log10 mean HPV-16 and HPV-18 binding ELISA antibody levels were somewhat higher in the AS04 group than in the aluminum hydroxide group. The sponsor also studied response to an inhibitory ELISA, and noted that for all 4 years of the study, log10 mean HPV-16 and HPV-18 ELISA inhibitory antibody levels were slightly higher in the AS04 group than in the aluminum hydroxide group.

Combined Analysis of long-term immune (4-years after dose 1) responses in subjects from HPV-004 and HPV-005

- **Summary Results:** Immune responses were pooled from subjects who received HPV 16/18 40 mcg adjuvanted with aluminum hydroxide alone or with AS04 and values compared. Both formulations were immunogenic and induced antigen-specific humoral responses, including antibodies that neutralized HPV-16 and HPV-18 in vitro. ELISA antibody titers to HPV-16 and HPV-18 were significantly higher in the AS04 group for up to 4 years after initiating the 3 doses vaccination series. Both formulations were immunogenic and induced significant specific CD4+ T-cell response. The functional characterization of the HPV specific CD4+ T-cells revealed that high frequency of IL-2 producing T cells with lymphoproliferative capacity

are induced and persist for months following HPV vaccination. There was some evidence that the AS04 adjuvant induces a somewhat higher memory B response directed against HPV-16 and 18 L1 than the aluminum hydroxide based vaccine (at 1 Month post III (Month 7). Pooled neutralization data from Month 7 to Year 4 of the HPV-16/18 vaccine were also presented. Both formulations induced antibodies that neutralized HPV-16 and HPV-18 in vitro. GMTs of neutralizing antibody titers to HPV-16 and HPV-18 were higher in the AS04 group as compared to the aluminum hydroxide group for up to 4 years after initiating the 3 dose vaccination series

Attachment #3 Phase IIb clinical studies

HPV-001: Proof of concept that Cervarix™ prevents incident infection with HPV 16 and/or 18 in naïve women (secondary persistent infection, abnormal cytology, immunogenicity, safety) compared to ALOH3 (N=560 HPV vaccine, N=553 aluminum hydroxide control; 15-25 yrs)

Study Dates: Study Dates: 1/3/01-4/30/03

Study Sites: 32 centers in Brazil, Canada and United States

Table 3 - HPV-001: Cohorts for analysis of efficacy (infection with HPV-16 and/or HPV- 18)

Cohort	Population
ATP (months 6-18)	Included ATP subjects who received 3 doses of vaccine, were seronegative for HPV 16 or HPV 18 at month 0 and were negative for high risk DNA at Month 0 and negative for HPV 16 or HPV 18 at Month 6 (post-dose 3 efficacy in ATP cohort)
ITT (months 0-27)	Included ITT subjects who received at least 1 vaccine dose, were negative for HR DNA at Month 0 (efficacy at post-dose 1 in ITT cohort)

Source: STN 125259/0, CSR 001, Table 11, p. 82

Efficacy Results in HPV-001: The primary endpoint of the study was prevention of HPV-16 and/or HPV-18 incident infection after three doses of vaccine during the period between months 6 to 18. In the ATP cohort for efficacy month 6-18, for cervical specimens alone, the point estimate of efficacy was 100% [95% CI: 79.4, 100%] for combined HPV 16 and/or 18 incident infection. The point estimate of efficacy for HPV 16 infection (91.6% [95% CI: 64.5, 98%]) reached statistical significance when considered alone, although not for HPV 18 individually due to a smaller number of cases (VE=72.3% [95% CI: -32.5, 94.3%]).

Table 4 - HPV-001: Vaccine efficacy against incident infection with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ATP cohort months 6-18)

Specimen Type	Infection Type	Attack Rate						Vaccine Efficacy
		Vaccine			Aluminum hydroxide control			% (95% CI)
		N	n	AR	N	n	AR	
Cervical specimens	HPV 16°	366	0	0.0	355	18	5.1	100 (79.4, 100%)
	HPV 18°	366	2	0.6	355	7	6.5	72.3% (-32.5, 94.2%)
	HPV 16 &/or 18°	366	2	0.6	355	23	6.5	91.6% (64.5, 98%)

N = number of subjects in specific cohort; n = number of subjects with at least one episode of incident infection with corresponding HPV type; AR = Attack rate = n / N; 95% CI = 95% confidence interval
p-value = result of comparison of attack rates between groups by Fisher's exact test (two sided)
° = without considering other HPV types
Source: STN 125259/0, CSR 001, from Tables 19, p. 109

In the Intent-to-treat (ITT) cohort [N=560 HPV vaccine and N=553 aluminum hydroxide control] (in which the entire 27 month period is considered), when cases of incident HPV 16 and/or HPV 18 infection in cervical specimens are counted after dose 1, the point estimates of efficacy are 83.0% (95% CI: 62.0, 92.4%); for combined HPV 16 and/or 18 incident infection; 82.7% (95% CI: 55.2, 93.3%); for incident HPV 16 infection; and 82.1% (95% CI: 38.8%, 94.7%) for incident HPV 18 infection. It is noted that because of the inclusion criteria, all subjects were naïve for high risk HPV types at baseline and had a normal Pap test, so this Intent-to-Treat cohort includes only HPV naïve subjects.

For one secondary endpoint (prevention of 6-month persistent infection with HPV 16 and/or 18) in the ATP cohort (months 6-18), the Vaccine Efficacy (VE) was 100% (95% CI: 47.0, 100%). There were however no cases of 6-month persistent infection with HPV 18 in either treatment group in this cohort.

Table 5 -HPV-001: Vaccine efficacy against persistent infection (2 positive specimens over a minimum of 6 months) with HPV-16, HPV-18 or with HPV-16 and/or HPV-18 for cervical specimens and all specimens (combined cervical and cervicovaginal specimens) (ATP cohort months 6-18)

Specimen Type	Infection Type	Attack Rate						Vaccine Efficacy
		Vaccine			Aluminum hydroxide control			% (95% CI)
		N	n	AR	N	n	AR	
Cervical specimens	HPV 16°	366	0	0.0	355	7	2.0	100% (47.0, 100%)
	HPV 18°	366	0	0.0	355	0	0.0	-
	HPV 16 &/or 18°	366	0	0.0	355	7	2.0	100% (47.0, 100%)

N = number of subjects in specific cohort
n = number of subjects with persistent infection with corresponding HPV type
AR = Attack rate = n / N
95% CI = 95% confidence interval
p-value = result of comparison of attack rates between groups by Fisher's exact test (two sided)
° = without considering other HPV types
Source: STN 125259/0, CSR 001, Table 23, p. 113

In the ITT cohort [N=560 HPV vaccine and N=553 aluminum hydroxide control] (in which the entire 27 month period is considered), when cases are counted after dose 1 from cervical specimens, the point estimates of efficacy are 95.1% [95% CI: 63.5, 99.3 for combined HPV 16 and/or 18 persistent infection (6 month definition); 93.9% [95% CI: 53.2, 99.2%] for persistent (6 month) HPV 16 infection; and 100% [95% CI: 24.4, 100%] for persistent 6 month HPV 18 infection.

There were very few CIN 2 cases detected at 27 months of study 001 in the ITT cohort, although all 3 cases accrued in the control group as compared to 0 in the HPV vaccine group. Vaccine Efficacy (VE) was not calculated for this secondary endpoint. In the ATP cohort for efficacy, one case of incident HPV 18 infection was detected in the vaccine treatment group at Month 12, although the CIN 1 lesion detected in this subject was associated with HPV 51 (which was present at Month 12). This study was not powered to detect a difference in prevention of CIN 2 or worse, and analyses of this endpoint is presented and discussed in study HPV-008.

The impact of genital infection and disease related to non-vaccine HPV types was difficult to assess in this study. Non-vaccine HPV types were combined in efficacy analyses, and when considered individually, co-infection with HPV 16 and/or 18 was not completely assessed. This issue will be discussed in context with study HPV-008.

Immunogenicity results in study HPV-001: Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the ITT (Total Vaccinated cohort).

According-To-Protocol (ATP) analysis of Immunogenicity: The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, and fulfilling requirements for analysis) for whom immunogenicity data were available (i.e. subjects for who assay results were available for antibodies at any blood sampling time-point). *Since subjects who acquired HPV-16 and/or HPV-18 infection during the trial were excluded from the ATP analysis,* CBER considered it important to review the results in the ITT cohort as well.

More than 98% of vaccinees were seropositive at one month following administration of the first vaccine dose. At one month following the administration of the full three dose vaccination course (month 7) all vaccinees were seropositive for HPV-16 and HPV-18. The administration of the third dose induced the greatest increase in antibody levels with geometric means titers (GMTs), and these GMTs were well above the levels observed in women with natural infections with HPV-18 and HPV-16. One year following the full vaccination course (month 18) all subjects in the vaccine group were seropositive for both HPV-16 and HPV-18 (including the one subject seronegative for HPV-18 at month 7). GMTs were still higher than those observed in women with natural HPV-16 or HPV-18 infections, respectively. Results in the ITT cohort were consistent with those in the ATP cohort.

Immune response by geographic region: GMTs in the North American population tended to be higher than for the population in Brazil, but there was no evidence of difference in efficacy between regions.

Safety Summary in study HPV-001: (Vaccine N=532, Control N=538)

- ***Solicited local adverse reactions in 7 days after vaccination:*** **A** statistically higher proportion of subjects reported a solicited local adverse reaction (including pain, swelling, and redness) after each dose in the 7 days after vaccination as compared to subjects in the aluminum hydroxide control group. Very few Grade 3 local adverse reactions were reported in the 7 days after vaccination. No apparent increase in local reactogenicity with progressive doses was reported, and local reactogenicity did not impact on compliance with completion of vaccine report cards.
- ***Solicited general adverse reactions in 7 days after vaccination:*** The most frequently reported solicited general symptoms (solicited general symptoms include fatigue, gastrointestinal symptoms, headache, itching, rash, temperature) reported in both groups were headache (62.3% of vaccine recipients and 61.2% of aluminum hydroxide control recipients) and fatigue (58% of vaccine recipients and 53.7% of aluminum hydroxide control recipients). Grade 3 symptoms occurred at low frequencies in both groups. The incidences of each solicited general symptom were comparable between the vaccine and control groups when calculated per subject. There was no evidence that the incidence of solicited general symptoms increased with subsequent doses. [Assessments of local and systemic adverse reactions are further detailed in study HPV-008 and study HPV-013].
- ***Unsolicited adverse reactions in 30 days after vaccination:*** The proportions of subjects with an unsolicited adverse reaction were comparable in the two treatment groups (47.3% vaccine, 48.5% control), as well the percentage of subjects with a grade 3 unsolicited adverse reaction (5.1% vaccine, 5.4% control).

- ***Unsolicited adverse reactions outside the 30 days after vaccination:*** The proportions of subjects with an unsolicited adverse reaction outside the 30 days after vaccination were also comparable in both groups (21.2% vaccine, 23.2% control).
- ***Deaths:*** There were no subject deaths in study HPV-001. However, there was one report of neonatal deaths (twins) in the control group in a center in North America. This case concerned the neonatal deaths of prematurely delivered (21 week gestation) twins with twin-twin transfusion syndrome. This event was considered as not related to the vaccination of the mother (PID ---(b)(6)----).
- ***Serious Adverse Reactions:*** The overall frequency of SAEs in each group was similar, with 22 subjects reporting at least one SAE in the HPV group and 19 subjects reporting at least one SAE in the control group. None of the SAEs were considered by the investigator to be causally related to vaccination.
- ***Adverse reactions Leading to Premature Discontinuation of Study Vaccine and/or Study:*** There were four withdrawals related to adverse events. One was a serious adverse event in the vaccine group (spontaneous abortion 132 days after the second dose of study vaccine), which the investigator considered as unrelated to vaccination and probably associated with natural causes. There were three withdrawals due to non serious adverse events in the control group (mental illness, fatigue and migraine, and dizziness).
- ***Clinical Laboratory Evaluations:*** Biochemical and hematology analyses were performed for subjects enrolled in centers 10, 17, 18, 23, 40, 70, 100 and 130. The hematology and biochemistry profiles were similar for both groups and there were no values out of range that were considered as medically relevant.
- ***Pregnancy:*** During the study 88 pregnancies (44 in the vaccine group, 44 in the placebo group) were reported. The number of pregnancy outcomes reported as miscarriages/spontaneous abortions was low and comparable between the two groups. There was one report of a neonatal death reported as an SAE. This case concerned the neonatal deaths of prematurely delivered (21 week gestation) twins with twin-twin transfusion syndrome. All reported complications were considered as not related to vaccination.

HPV-007: Long term efficacy in prevention of HPV 16 and/or 18 incident infection (secondary persistent infection – 6 & 12 months, abnormal cytology, immunogenicity, safety) (N=393 C= 383 AlOH3; females from HPV-001). The duration of the additional follow-up was 36 months from time of enrollment into extension study (represented follow-up of subjects from study HPV-001 out to 6.4 years).

Efficacy results for HPV-007: Statistically significant vaccine efficacy was observed against incident virological and histopathological endpoints associated with HPV-16 and or HPV-18 infection up to approximately 6 years post vaccination:

- Incident infection with HPV-16 and/or HPV-18 (primary objective): VE = 96.7% [87.4%, 99.6%], ATP cohort vaccine group [47 subjects in the control group and 2 in the vaccine group]
- 6-month persistent infection with HPV-16 and/or HPV-18: VE = 100% [85.9%, 100%], ATP cohort [0 cases in the vaccine group and 24 in the control group]
- 12-month persistent infection with HPV-16 and/or HPV-18: VE = 100% [75.0%, 100%], ATP cohort [0 cases in the vaccine group and 15 in the control group; statistical significance for HPV 16 although the case split for HPV-18 was 0 in the vaccine group and 4 in the control group]
- CIN1+ associated with HPV-16 and/or HPV-18: VE = 100% [52.6%, 100%], Total cohort [0 cases in the vaccine group, 9 in the control group; statistical significance for HPV 18 alone not

reached although there were 0 cases in the vaccine group related to HPV-18 and 3 in the vaccine group]

- CIN2+ associated with HPV-16 and/or HPV-18: VE = 100% [19.7%, 100%], Total cohort [0 cases in the vaccine group and 6 cases in the control group; point estimates for CIN 2+ associated with HPV-16 or HPV-18 individually did not reach statistical significance, but study not powered for this objective.]

Immunogenicity results for HPV-007: 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 vaccinees in the According to Protocol (ATP) population for Immunogenicity remained seropositive for both HPV-16 and HPV-18 IgG antibodies 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 evidence of apparent further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76). Seropositvity rates and GMTs were very similar in the Total Vaccinated Cohort as compared to the ATP cohort for immunogenicity out to Months 69-74 and Months 76-76. GMTs in the vaccine group were much higher than subjects in the control group and persisted through Month 76.

No breakthrough cases of **persistent HPV-16/18 infection** (6-month and 12-month definition) were observed in the vaccine group during studies HPV-001 and HPV-007. However, three cases of breakthrough HPV-**16/18 incident infection** were reported in the vaccine group. The ELISA titers obtained for these subjects with breakthrough infection were provided. In two subjects, when compared to subjects in the ATP cohort for immunogenicity, the GMTs for anti-HPV 16 and 18 were lower throughout the study period as compared to subjects who did not develop an infection with either HPV 16 or HPV 18. The third subject's GMTs were somewhat lower for HPV 16 initially, but were higher than GMTs in the ATP cohort at the later time points, so there was no consistent pattern noted in these subjects with "breakthrough" cases. Because of the low number of subjects with breakthrough cases, and lack of consistent pattern in subjects with a breakthrough case, an immune correlate of protection was not possible to identify. It is difficult to state that the GMTs associated with natural infection is the protective level given the variability in these results.

Anti-HPV-16/18 neutralizing antibodies measured by pseudovirion neutralization assay: The seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 pseudovirion neutralizing antibodies in a subset of subjects were presented. GMT levels for both HPV-16 and HPV-18 by assays for pseudovirion neutralizing antibodies showed a plateau that began approximately at Month 18 post vaccination and was sustained for up to 76 months of follow-up. Seropositivity rates for both HPV-16 and HPV-18 (≥ 98.0%) were similar to those observed with ELISA (≥ 98.6%).

Regarding immune responses to non-vaccine HPV types, although the anti-HPV 31 IgG seropositivity rates were > 80% and HPV-45 IgG seropositivity rates in vaccine recipients were > 83.7% at Month 24, the seropositivity rate for PSV neutralizing antibodies for HPV-31 reached a peak of 47.6% seropositivity rate at Month 7 and was 0% by Month 45-50. For HPV-45, the seropositivity rate for PSV neutralizing antibodies reached a peak of 9.5% at Month 7 and was 0% at Month 45-50 in a subset of subjects who were followed from study HPV-001 to study HPV-007. This observation may indicate that the immune response to non-vaccine HPV types HPV-31 and HPV-45 may be less robust and shorter in duration as compared to the immune response elicited for HPV 16 and HPV 18.

Geographic variation in immune responses: The GMTs for HPV 16 and 18 were numerically higher for both HPV 16 and 18 in North America as compared to Brazil. However, the 95% CIs around the GMTs were overlapping, and no difference in efficacy was noted.

Safety at end of study HPV-007 (total 6 years follow-up from study HPV-001):
Adverse Reactions: In the ATP cohort for safety, **t**he proportion of subjects with an adverse reaction during the entire study period was 28.4% in the vaccine group and 33.3% in the control group. (In the Total Vaccinated cohort, the proportions are similar to the ATP cohort for safety (28% vaccine, and 32.9% control group).

New Onset Chronic Diseases (NOCDs) were reported by 18/373 (4.8%) of vaccine recipients and by 21/369 (5.7%) of aluminum hydroxide control recipients over the entire study period. (NOCDs were defined as illnesses such as diabetes mellitus, autoimmune diseases, allergies, asthma, and other conditions prompting either emergency room visits or physician visits that are **not related to common diseases** throughout the entire study period. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, vaginitis, vulvitis, menstrual cycle abnormalities and injury.) (See Attachment 1 for list of NOCDs and MedDRA codes).

New Onset Autoimmune Diseases (NOADs) were reported in a total of six subjects during the entire study period, for two subjects (0.5%) in the vaccine group and four subjects (1.1%) in the control group. (NOADs were based on a pre-defined list of potential autoimmune events which excluded allergy related events or isolated signs and symptoms and events not considered as strictly of autoimmune origin, a GSK Biologicals physician reviewed the AEs identified as NOCDs and classified as "New Onset of Autoimmune Diseases".

Serious Adverse Reactions: 31/373 (7.9%) SAEs were reported in the vaccine group and 39/369 (10.2%) were reported in the control group.

Pregnancy: During the entire study period, a total of 261 pregnancies (130 in the vaccine group and 131 in the placebo group) were reported for 217 subjects. The number of pregnancies not resulting in delivery of a normal, healthy infant was similar or lower in the vaccine compared to the placebo group. A total of 19 cases of spontaneous abortion, abnormal infant, elective termination, missed abortion or still birth were observed in the vaccine group compared to 29 cases in the control group. None of the abnormal pregnancy outcomes reported as SAE were considered as related to vaccination by the investigator. It is noted that over approximately 76 months of follow-up, overall, the rates of spontaneous abortions were higher in the control group (15/131 or 11.5%) as compared to the vaccine group (10/130 or 7.7%). Overall spontaneous abortion rates will be reviewed for all Cervarix™ studies.

Attachment #4 Summary of Lot consistency studies HPV 012 and 016
HPV-012: A phase III, double-blind, randomized study to assess the consistency of the immunogenicity of three consecutive production lots of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects aged 10 – 25 years and to demonstrate non-inferiority of the candidate HPV vaccine manufactured using different production processes.
Study Dates: 9/4/04-7/15/05
Study Sites: 17 centers in 6 countries (Denmark, Estonia, Finland, Greece, The Netherlands and Russia).

Three groups were vaccinated in the study:

- Three groups (150 subjects per group) of women aged 15-25 years received one of three consecutive production lots of the industrial scale HPV-16/18 L1/AS04 vaccine (i.e. ----------(b)(4)----------produced vaccine) [Groups Lot 1 (---(b)(4)---), 2 (-(b)(4)-) and 3 (-(b)(4))-].
- The fourth group (150 subjects) of women aged 15-25 years received the --(b)(4)---produced HPV vaccine (Group ----(b)(4)----).
- The fifth group (150 subjects) of pre-teen and adolescent women (aged 10-14 years) received the ---(b)(4)-----produced HPV vaccine (Group [10-14]).

Immunogenicity Results of HPV-012: All objectives were met.

- The three lots of vaccine which were compared were consistent in eliciting anti-HPV 16 and anti-HPV 18 antibodies as measured by ELISA (met pre-defined limits [---(b)(4)-----]).
- ---(b)(4)--- and ---(b)(4)--- vaccine lots were consistent in elicit antibodies to anti-HPV 16 and anti-HPV 18 as measured by ELISA (<10% difference in seroconversion rates and upper limits of 95% CI were < 2).
- Anti-HPV 16 and anti-HPV 18 IgG antibodies elicited in females 10-14 years of age were non-inferior to the antibodies in females 15-25 years of age (<10% difference in seroconversion rates and upper limits of the 95% CI were < 2).
- The ---(b)(4)-- produced vaccine was consistent in anti-HPV 16 and anti-HPV 18 IgG antibodies elicited as compared to the antibodies elicited in HPV-001 (difference in seroconversion < 10% and upper limits of the 95% CI less than 2).
- Results were similar in the Total Vaccinated Cohort.

Safety summary for study HPV-012

- The three consecutive production lots of HPV-16/18 vaccine (-(b)(4)- process) were similar in terms of reactogenicity.
- The reactogenicity profile of HPV-16/18 produced using the (b)(4) process was similar to that of the vaccine produced using the (-(b)(4)- process.
- There was little difference in the reactogenicity and safety profile of the HPV-16/18 vaccine (-(b)(4)- -produced) in 15-25 year old subjects and 10-14 year old subjects, except for a tendency observed in the younger subjects to report fewer unsolicited symptoms. Few new onset chronic diseases were identified.

Study HPV-016: A phase III, double-blind, randomized study to assess the consistency of the immunogenicity of three production lots of GlaxoSmithKline Biologicals' HPV-16/18 L1/AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects aged 18 – 25 years and to demonstrate non-inferiority of the candidate HPV vaccine manufactured at -(b)(4)- L scale compared with a lower ((b)(4) L) manufacturing scale.

Study Dates: 10/28/05-9/8/06

Study Sites: Nine centers in three countries: Denmark, Lithuania, and Poland.

There were several treatment groups:

- Three groups of subjects were to receive one of the three –(b)(4)-L scale production lots of the HPV-16/18 L1 AS04 vaccine.
- The fourth group of subjects was to receive the –(b)(4)-L scale production lot of the HPV-16/18 L1 AS04 vaccine.

Immunogenicity conclusions study HPV-016:

- One month after the third dose of study vaccine (Month 7), the three -(b)(4)-L vaccine lots were demonstrated to be consistent in terms of immunogenicity (GMTs) for both anti-HPV-16 and anti-HPV-18 antibodies.

- The HPV vaccine produced at -(b)(4)L manufacturing scale was demonstrated to be non-inferior to the HPV vaccine produced at -(b)(4)-L scale in terms of seroconversion rates and GMTs one month following the administration of the third dose of study vaccine (Month 7).
- One month after the third dose of study vaccine, 100% of subjects had seroconverted for both HPV-16 and HPV-18 antigens with high GMT values.

Safety conclusions for study HPV-016: No specific imbalances were noted in comparison of the different vaccine lots used in this study.

Attachment #5 Pooled Safety Analyses

Table 33 - Deaths reported throughout all studies involving Cervarix™ (DLP 8/31/08) [CBER generated]

General term	Cervarix™ N=33623 (time to onset)	Control N=23700 (time to onset)
Cardiac disorders	1 (16 months)	1 (2.2 months)
Immune mediated illnesses and complications	3 (3.2 months)	1 (6 months)
Death (not specified)	0	2 (only 1 specified-36 months)
Infections	3 (18.7 months)	1 (22 months)
Neoplasms	3 (16 months)	2 (4.9 months)
Psychiatric disorders	1 (3.4 months)	5 (11.7 months)
Pulmonary embolus with lung mass (?CA or TB)	1 (24 months)	0
Trauma	8 (20.3 months)	7 (13.4 months)
Total	20 (0.06%)	18 (0.08%)

Individual and mean times to first event after any dose in months are included in parentheses.

Table 34 - Percentage of subjects reporting the occurrence of at least one serious adverse event in the update of the pooled safety analysis in the BLA submission (3/07) (Total vaccinated cohort)

Follow-up period	HPV N=16142	Alu N=3454	HAV 360 N=1032	HAV 720 N=9325	Pooled control N=13811
Vaccination period (Month 0-Month 7)	206 (1.3%)	35 (1.0%)	14 (1.4%)	131 (1.4%)	180 (1.3%)
Entire observation period	851 (5.3%)	84 (2.4%)	26 (2.5%)	699 (7.5%)	809 (5.9%)

Studies HPV-001, HPV-003, HPV-004, and HPV-005, HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014 Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016 Age groups: HPV = [10-14], [15-25] and [25+], ALU = [15-25] and [25+], HAV360 = [10-14] and HAV720 = [15-25]
N = number of subjects with at least one administered dose; n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: STN 125259.48, supplemental safety update, Table 19, p. 72

Table 35 - Percentage of subjects reporting the occurrence of at least one serious adverse event in the update of the pooled safety analysis in the BLA submission (3/07) and in the cumulative analysis of all studies in which Cervarix™ has been administered (Total vaccinated cohort)

Data set	Reporting period	HPV group	Pooled control group
Pooled analysis	**Vaccination period (Month 0-Month 7)**	1.3% (1.1, 1.5%)	1.3% (1.1, 1.5%)
	Entire observation period	5.3% (4.9, 5.6%)	5.9% (5.5, 6.3%)
All studies	**Vaccination period (Month 0-Month 7)**	1.2% (1.1, 1.3%)	1.3% (1.2, 14%)
	Entire observation period	5.5% (5.2, 5.8%)	6.9% (6.5, 7.1%)

Pooled analysis: Studies HPV-001, HPV-003, HPV-004, and HPV-005, HPV-007 [final analysis], HPV-008 [final analysis], HPV-012, HPV-013, HPV-013 Ext [Month 18 analysis], HPV-014, HPV-014 Ext [Month 18 analysis], HPV-015 [Month 7 safety interim analysis] and HPV-016; Age groups: HPV = [10-14], [15-25] and [25+], Pooled Control = [10-14], [15-25] and [25+]; All studies: all studies in which Cervarix™ has been administered (data lock-point of August 31, 2008).
Age groups: HPV = [9-14], [15-25] and [25+], Pooled Control = [9-14], [15-25] and [25+]; n/% = number/percentage of subjects reporting at least once the symptom; =95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

In general, the proportions of subjects with SAEs across these studies are comparable in incidence both during the vaccination phase of the study and throughout the entire study period,

and proportions of SAEs when categorized by System Organ Class in each of these time periods are comparable.

Table 36 - Pooled safety analysis: percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class, during the vaccination period (Month 0 - Month 7) (Total vaccinated cohort) [INCLUDES ALL STUDIES SUBMITTED TO THE BLA TO SUPPORT LICENSURE]

Primary System Organ Class	HPV N=16142	Control N=13811
At least one symptom	206 (1.3%)	180 (1.3%)
Blood and lymphatic system disorders	0 (0.0%)	3 (0.02%)
Cardiac disorders	4 (0.02%)	0 (0.0%)
Congenital, familial and genetic disorders	1 (0.006%)	2 (0.01%)
Ear and labyrinth disorders	0 (0.0%)	2 (0.01%)
Endocrine disorders	1 (0.006%)	1 (0.007%)
Eye disorders	1 (0.006%)	0 (0.0%)
Gastrointestinal disorders	23 (0.1%)	10 (0.1%)
General disorders and administration site conditions	2 (0.001%)	2 (0.01%)
Hepatobiliary disorders	5 (0.03%)	6 (0.04%)
Immune system disorders	1 (0.006%)	5 (0.04%)
Infections and infestations	62 (0.4%)	61 (0.4%)
Injury, poisoning, and procedural complications	21 (0.1%)	19 (0.1%)
Investigations	0 (0.0%)	2 (0.01%)
Metabolism and nutrition disorders	4 (0.02%)	3 (0.02%)
Musculoskeletal and connective tissue disorders	3 (0.02%)	2 (0.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (0.05%)	7 (0.1%)
Nervous system disorders	11 (0.1%)	5 (0.04%)
Pregnancy, puerperium and perinatal conditions	27 (0.2%)	20 (0.1%)
Psychiatric disorders	11 (0.1%)	17 (0.1%)
Renal and urinary disorders	2 (0.001%)	1 (0.007%)
Reproductive system and breast disorders	10 (0.1%)	12 (0.1%)
Respiratory, thoracic and mediastinal disorders	4 (0.02%)	7 (0.1%)
Skin and subcutaneous tissue disorders	2 (0.001%)	2 (0.01%)
Surgical and medical procedures	2 (0.001%)	3 (0.02%)
Vascular disorders	4 (0.02%)	1 (0.01%)

Pooled control = ALU+HAV360+HAV720

Table 37 - Pooled safety analysis: percentage of subjects reporting SAEs classified by MedDRA Primary System Organ Class, during the entire follow-up period (Total vaccinated cohort) INCLUDES STUDIES WHICH WERE SUBMITTED TO THE BLA TO SUPPORT LICENSURE

Primary System Organ Class	HPV N=16142	Control N=13811
At least one symptom	851 (5.3%)	809 (5.9%)
Blood and lymphatic system disorders	6 (0.04%)	7 (0.05%)
Cardiac disorders	11 (0.1%)	4 (0.03%)
Congenital, familial and genetic disorders	2 (0.01%)	3 (0.02%)
Ear and labyrinth disorders	2 (0.01%)	5 (0.03%)
Endocrine disorders	4 (0.02%)	3 (0.02%)
Eye disorders	3 (0.02%)	1 (0.007%)
Gastrointestinal disorders	61 (0.4%)	54 (0.4%)
General disorders and administration site conditions	5 (0.03%)	5 (0.03%)
Hepatobiliary disorders	26 (0.2%)	22 (0.2%)
Immune system disorders	6 (0.04%)	10 (0.1%)
Infections and infestations	247 (1.5%)	236 (1.7%)
Injury, poisoning, and procedural complications	99 (0.6%)	97 (0.7%)
Investigations	0 (0.0%)	2 (0.01%)
Metabolism and nutrition disorders	9 (0.1%)	7 (0.05%)
Musculoskeletal and connective tissue disorders	22 (0.1%)	12 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (0.1%)	21 (0.2%)

Nervous system disorders	44 (0.3%)	23 (0.2%)
Pregnancy, puerperium and perinatal conditions	246 (1.5%)	232 (1.7%)
Psychiatric disorders	46 (0.3%)	49 (0.4%)
Renal and urinary disorders	8 (0.05%)	7 (0.05%)
Reproductive system and breast disorders	44 (0.3%)	45 (0.3%)
Respiratory, thoracic and mediastinal disorders	18 (0.1%)	19 (0.1%)
Skin and subcutaneous tissue disorders	5 (0.03%)	5 (0.03%)
Surgical and medical procedures	9 (0.1%)	9 (0.1%)
Vascular disorders	9 (0.1%)	9 (0.1%)

Pooled control = ALU+HAV360+HAV720