Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Human Papillomavirus Vaccine Types 16 and 18 (recombinant, AS04 adjuvanted)

Proprietary Product Name: Cervarix

Sponsor: GlaxoSmithKline Pty Ltd

June 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (Extension of indications)
Decision:	Approved
Date of Decision:	23 March 2011
Active ingredient(s):	Human Papillomavirus Vaccine Types 16 and 18 (recombinant, AS04 adjuvanted)
Product Name(s):	Cervarix
Sponsor's Name and Address:	GlaxoSmithKline Australia Pty Ltd
	436 Johnston St, Abbotsford VIV 3067
Dose form(s):	Solution for injection
Strength(s):	20 µg each of HPV-16 L1 and HPV-18 L1 proteins per 0.5 mL dose
Container(s):	Glass vial and syringe
Approved Therapeutic use:	In females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations.
Route(s) of administration:	Intramuscular (IM)
Dosage:	0.5 mL
ARTG Number (s)	126114 and 126115

Product Background

GlaxoSmithKline Biologicals (GSK) developed a prophylactic HPV-16/18 L1 AS04 vaccine (Cervarix) for the prevention of premalignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. Cervarix was registered in Australia on 18 May 2007, in the European Union on 20 September 2007 and is currently licensed for use in more than 90 countries worldwide. Cervarix is currently licensed in Australia for "*the prevention of cervical cancer (squamous-cell carcinoma and adenocarcinoma) by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN1 and pre-cancerous lesions (CIN2 and CIN3) caused by oncogenic Human Papillomavirus (HPV) Types 16 and 18*. The vaccination course consists of three doses administered via intramuscular (IM) injection and the recommended schedule is 0, 1, 6 months.

The sections of the Product Information (PI) to be specifically affected according to this application are:

Indications

Change the indication to 'the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic Human Papillomaviruses (HPV); that is, removing the specific mention of HPV types 16 and 18.

Dosage and administration

The addition of a sentence concerning flexibility of the vaccination schedule around the third dose is proposed.

Warnings and Precautions

The sponsor proposes to specify that Cervarix does not provide protection against all oncogenic HPV types.

Pharmacodynamics (Clinical Studies)

GSK proposes to extensively update the efficacy and immunogenicity based on recent data from Study HPV-008.

The currently approved indication is as follows:

> Cervarix is indicated in females from 10 to 45 years of age for the prevention of cervical cancer by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3) caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations.

The sponsor is seeking to modify and expand the indication to encompass non-vaccine oncogenic HPV types as follows:

> Cervarix is indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomaviruses (HPV). Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations (see Precautions and Clinical Trials).

Regulatory Status

The overseas regulatory status of Cervarix is summarised below.

Table 1:

Overseas Regulatory status of Cervarix:

Country	Approval date
Canada	3 February 2010
European Union (EU)	9 August 2010
Singapore	15 June 2010
Switzerland	4 March 2010

Product Information

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There were no quality data submitted with this application.

III. Nonclinical Findings

There were no nonclinical data submitted with this application.

IV. Clinical Findings

Introduction

This application includes data and final reports from the previously evaluated Phase III clinical studies (HPV-008 and HPV-007) to support changes in the product information and update it with final report data. Based on the updated data an extension of indication is sought regarding protection against non-vaccine oncogenic HPV-types. Included also is one new study (HPV-042) of concomitant administration of Cervarix and dTpa-IPV vaccine to support the integration of Cervarix into childhood vaccination schedules.

Pharmacokinetics

Pharmacokinetic studies are not relevant for this extension application but some background to the vaccine is included here for completeness. The dosage of the HPV-16/18 L1 AS04 vaccine was selected based on the results from nonclinical and clinical immunogenicity studies described in the initial Marketing Authorisation Application (March 2006). The HPV-16/18 L1 AS04 vaccine contains 20µg per 0.5 mL dose of HPV-16 L1 protein and 20µg per 0.5ml dose of HPV-18 L1 protein assembled as virus-like particles (VLPs) as active ingredients. The L1 proteins are formulated with GSK's AS04 adjuvant system, which is composed of 50µg of monophosphoryl lipid (MPL) and 500µg of aluminum hydroxide salt. The vaccine is preservative-free. The vaccine meets the World Health Organization (WHO) requirements for the manufacture of biological substances of HPV vaccine.

Drug Interactions

No new data were submitted under this heading.

Pharmacodynamics

No new data were submitted under this heading.

Efficacy

The studies submitted to support this application are well designed Phase III, randomized, controlled, multi-centre studies. Study HPV-007 is the long-term follow-up of vaccine efficacy, immunogenicity and safety of the primary study, HPV-001. The HPV-007 (Month 36) study report provides additional efficacy, immunogenicity and safety data, and represents significant long-term follow-up after the first dose administered to women in the primary study, HPV-001 (up to 6.4 years; approximately 77 months). Study HPV-007 (Month 36 analysis) is also an extension of HPV-001. In the initial clinical development program for Cervarix, adolescent girls and women aged 15 to 25 years received three doses of Cervarix according to a 0, 1, 6 month schedule in the primary Study HPV-001 conducted in North America and Brazil. Vaccine efficacy, immunogenicity and safety parameters were evaluated up to Month 27 in HPV-001 and continued to be followed-up for an additional three years in Study HPV-007. Two interim analyses (Month 12 and Month 24) and the final analysis of Study HPV-007 (Month 36) are now completed and included in the submitted data in this application. The final reports of HPV-008 and HPV-042 are also included. Study HPV-008 is a large, Phase III, multi-centre, double blind, study assessing efficacy, immunogenicity and safety of HPV-16/18 L1 AS04 in the prevention of persistent HPV-16 or HPV-18 cervical infection and cervical intraepithelial neoplasia (CIN) in female adolescents and young adult women, 15 to 25 years of age (using Hepatitis A vaccine as control. Study HPV-042 assessed the immunogenicity and safety of dTpa-IPV co-administered with Cervarix and compared it to separate administration, in healthy female subjects aged between 10 and 18 years.

Main Clinical Studies

Study HPV-007

HPV-007 was three year additional follow-up of vaccine efficacy and immunogenicity in subjects who had been previously vaccinated with three doses of Cervarix in Study HPV-001 (a Phase IIb, double-blind, randomised, multi-centre, controlled study conducted in North America and Brazil).

Methods

Subjects were screened at HPV-001 study entry and were only eligible if they were seronegative for HPV-16 and HPV-18 antibodies by Enzyme-Linked Immuno-Sorbent Assay (ELISA) and HPV deoxyribonucleic acid (DNA) negative for high-risk (HR) HPV types by polymerase chain reaction (PCR). A total of 776 subjects from Study HPV-001 were enrolled in HPV-007. No vaccine was administered during this extension study. This submission describes the efficacy data collected during the third year of extended follow-up in HPV-007 and provides an additional 12 months of efficacy data (up to 77 months) and immunogenicity data (up to 76 months follow-up) after the first dose in HPV-001.An overview of the study design is shown in Figure 1.

Blinding

Blinding was maintained for all subjects, investigators and investigators' study staff with regard to the individual subject treatment assignments allocated in Study HPV-001. GSK personnel directly involved in the conduct of this study were also blinded to the individual subject treatment.

Statistical methods

The Conditional Exact Method and confirmatory Cox regression analysis were performed. The analyses were performed by an external statistician.

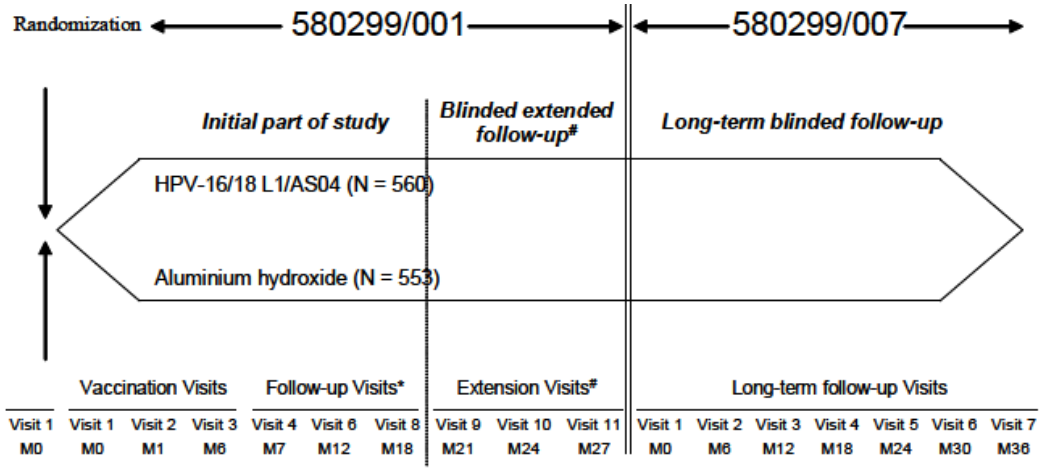
- **Primary endpoint**
  - Incident cervical infection with HPV-16 and/or HPV-18.
- **Secondary endpoints**
  - Persistent cervical infection (6-month definition) with HPV-16 and/or HPV-18.
  - Persistent cervical infection (6-month definition) with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
  - Incident cervical infection with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
  - Histopathologically-confirmed CIN1+ or CIN2+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen (by PCR).
  - Histopathologically-confirmed CIN1+ or CIN2+ associated with any/each
  - Oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) detected within the lesion of the cervical tissue specimen (by PCR). CIN1+ was defined as CIN1, CIN2, CIN3, adenocarcinoma *in situ* (AIS) and invasive cervical cancer. CIN2+ defined as CIN2, CIN3, adenocarcinoma *in situ* (AIS) and invasive cervical cancer.
  - Abnormal cytology (Atypical squamous cells of undetermined significance (ASC-US), Low-grade squamous intraepithelial lesion (LGSIL or LSIL), Atypical squamous cells - cannot exclude HSIL (ASC-H), Atypical Glandular Cells (AGC), Atypical squamous cells, high grade lesion (ASC-H)) associated with an HPV-16 and/or HPV-18 cervical infection.

- Abnormal cytology (ASC-US, LSIL, HSIL, AGC, ASC-H) associated with any/each oncogenic HPV type (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) cervical infection.

· **Other endpoints**

- Persistent cervical infection (12-month definition) with HPV-16 and/or HPV-18.
- Persistent cervical infection (12-month definition) with any oncogenic HPV type HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68).
- Pattern of HPV-16 and/or HPV-18 detection in cervical specimens collected after detection of an incident cervical infection in Study HPV-001 or Study HPV-007.
- HPV-16 and HPV-18 antibody titres (by ELISA) in all study subjects, and V5/J4 monoclonal antibody inhibition tests (indicative of HPV-16 and HPV-18 Seroconversion) and/or neutralizing antibody assay in subsets of subjects.
- Occurrence of serious adverse events (SAEs), new onset chronic disease (NOCDs; for example diabetes mellitus or autoimmune diseases) and other conditions prompting either emergency room visits or physician visits that were not related to common diseases throughout the entire study period (see safety)
- Time-to-occurrence of cervical infection with HPV-16 or HPV-18.
- Histopathologically confirmed vulval intraepithelial neoplasia (VIN) or vaginal intraepithelial neoplasia (VaIN) associated with oncogenic HPV type detected in the lesional component of the tissue (by polymerase chain reaction (PCR).

Figure 1: Overview of study design



Notes:
The blinded extended follow-up phase of the 580299/001study involved only those subjects who completed their month 18 visit (Visit 8) before 1 February 2003. Month 27 refers to the maximum duration of follow-up in the 580299/001 cohort.
* Visits 5 (M9) and 7 (M15) for study 580299/001 are not shown. These visits to the 580299/001 study site were optional, however, the collection of self-obtained cervical vaginal specimens was required.

Sample size

Of the 1113 subjects initially enrolled in Study HPV-001, all subjects whom the investigator could contact and who were eligible were to participate in this study. Based on an assumption of the occurrence of incident HPV-16 and/or HPV-18 cervical infection in North America (USA and Canada) and Brazil = 3.5% over 12 months. A calculated sample size of 500 gave approximately 80% power to detect a vaccine efficacy level of 70%.

Study cohorts/data sets analysed

Data evaluations were performed on two defined study cohorts: According-to-protocol (ATP) cohort and Total cohort. The purpose of the two analyses was to ensure that protocol violations, subject dropouts and withdrawals were not treatment related and did not lead to any selection bias in the efficacy results. For virological endpoints, analyses were performed on the ATP cohort for efficacy (primary analysis) and on the Total cohort. For cytological and histopathological endpoints, however, the efficacy analysis performed on the Total cohort was considered as primary, due to the limited number of cases obtained during this study. The ATP cohort for efficacy supplemented the analysis of these endpoints.

ATP cohort for analysis of efficacy

The ATP cohort for analysis of efficacy included all subjects for whom differential treatment effect on efficacy was likely (that is, those meeting all eligibility criteria in Studies HPV-001 and HPV-007), complying with the procedures defined in the HPV-001 and HPV-007 protocols, and for whom data concerning efficacy endpoints were available.

ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity included all evaluable subjects (that is, those meeting all eligibility criteria in Studies HPV-001 and HPV-007, complying with the procedures defined in the HPV-001 and HPV-007 protocols and fulfilling requirements for analysis) for whom data concerning immunogenicity were available for at least one study vaccine antigen component and at least one blood-sample.

Total cohort

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

Results

Enrolment

A total of 776 subjects were enrolled in Study HPV-007: 393 subjects who received the HPV-16/18 L1/AS04 vaccine and 383 subjects who received the placebo control (in Study HPV-001). Subjects were enrolled at 28 centres in Brazil (448 subjects) and North America (United States and Canada) (328 subjects). Overall, 700 of the 776 enrolled subjects (90.2%) completed the study. The mean follow-up period from the start of Study HPV-001 until the end of Study HPV-007 (Month 36) was 5.9 years, that is, 2164.1 days (standard deviation (SD) of 98.31 days), with a maximum duration of 6.4 years, that is, 2341.0 days. The mean follow-up period from Month 6 (after completion of vaccination) of Study HPV-001 until the end of Study HPV-007 (Month 36) was approximately 5.5 years (66 months), that is, 1987.0 days (standard deviation of 97.76 days). Of those enrolled, 76 withdrew prematurely, 34 were in the vaccine group and 42 were in the placebo group (see Table 2). The main reasons for withdrawal were unrelated to the vaccine.

Table 2: Number of subjects enrolled, completed and withdrawn with reason for withdrawal (Total cohort)

	Vaccine	Placebo	Total
Number of subjects enrolled	393	383	776
Number of subjects completed	359	341	700
Number of subjects withdrawn	34	42	76
Reasons for withdrawal :			
Serious Adverse Event	0	0	0
Non-serious adverse event	0	0	0
Protocol violation	3	2	5
Consent withdrawal (not due to an adverse event)	7	10	17
Migrated/moved from study area	4	6	10
Lost to follow-up	16	18	34
Others	4	6	10

Vaccine = HPV-16/18 L1/AS04 (DVLP017A) Placebo = Aluminium hydroxide (DVLP018A)

Demographics

The demographic profile of the vaccine and placebo groups was similar with respect to age, racial distribution, height and weight. Overall, the mean age at HPV-007 study entry was 23.2 years in each group and the population was diverse with respect to racial distribution.

Efficacy - Primary and Secondary Outcomes

Vaccine efficacy was demonstrated against incident infections, persistent infections with HPV-16 and/or HPV-18 from the combined (pooled) analyses of Studies HPV-001/HPV-007. Despite sustained exposure of subjects to HPV natural infection, very few breakthrough cases of HPV-16/18 infection (6-month or 12-month definitions) were seen in the vaccine group for up to 6.4 years of follow-up after the first dose. The cumulative vaccine efficacy over 6.4 years for incident HPV-16/18 infections in the ATP cohort was 95.3% (95% CI: 87.4%, 98.7%). The cumulative vaccine efficacy for persistent HPV-16/18 infections in the total cohort was 98.2% (95% CI: 89.5%, 100%) and for 12M+ persistent HPV-16/18 infections (persistent for longer than 12 months) was 96.9% (95% CI: 81.4%, 99.9%) over 6.4 years (Table 3). Vaccine efficacy against any cytological abnormality (≥ASC-US) associated with HPV-16 and/or HPV-18 was 96.7% [87.3%, 99.6%] over 6.4 years of follow-up. Vaccine efficacy against CIN1+ associated with HPV-16 and/or HPV-18 was 100% [73.4%, 100%]. Vaccine efficacy against CIN2+ associated with HPV-16 and/or HPV-18 was 100% [51.3%, 100%] up to 6.4 years after the first dose (see Table 4).

In summary, statistically significant long-term vaccine efficacy was observed against all virological and cytological endpoints, with the exception of HSIL, as there was only one case overall (in placebo group) and histopathological endpoints associated with HPV-16 and or HPV-18 infection for approximately 6 years post vaccination.

Table 3: Cumulative vaccine efficacy against HPV-16 and/or HPV-18 persistent infections over 6.4 years (cervical samples only, Total cohort)

Event Type	Group	N	n	VE		
				%	LL	UL
6 Month Persistent Infection						
HPV-16/18	Vaccine	481	1	98.2	89.5	100.0
	Control	470	50	-	-	-
12 Month Persistent Infection						
HPV-16/18	Vaccine	481	1	96.9	81.4	99.9
	Control	470	30	-	-	-

Vaccine = HPV-16/18 L1/AS04 (DVLP017A); Control = Aluminium hydroxide (DVLP018A)
N = number of subjects included in each group
Subjects with an event who did not report the same event in HPV-001
n = number of subjects reporting at least one event in each group
Subjects with an event are DNA negative for HPV-16 and HPV-18 at Month 0 and Month 6 in HPV-001
Follow-up period starts at Month 0 for HPV-001 and pooled HPV-001/007, interval period between end of HPV-001 and beginning of HPV-007 is censored
LL, UL = 95% Lower and Upper confidence limits; VE(%) = Vaccine Efficacy (Conditional exact method)

This is shown diagrammatically in Figure 2.

Figure 2: Kaplan-Meier curves for incident infection with HPV-16 and/or HPV-18 (Combined [pooled] HPV-001/007, Cervical samples only, ATP cohort for efficacy)

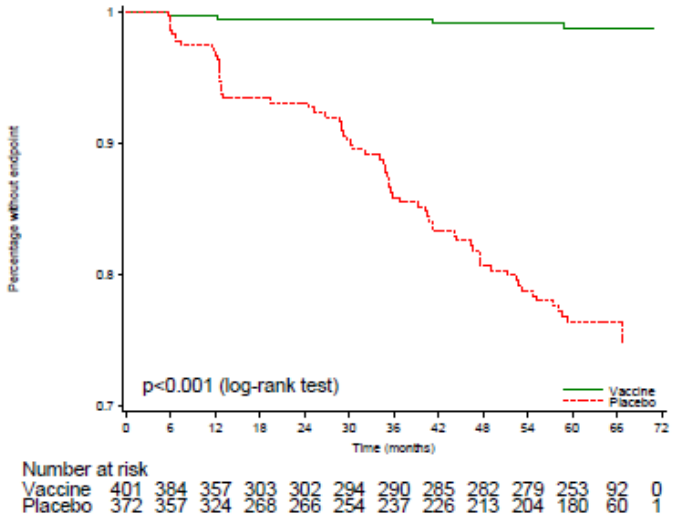


Table 4: Cumulative vaccine efficacy against HPV-16 and/or HPV-18 cytological and histopathological endpoints over 6.4 years (Total cohort)

HPV types	Endpoint	Vaccine		Control		VE by Conditional exact		
		N	n	N	n	%	LL	UL
HPV-16/18	≥ASC-US	505	2	497	54	96.7	87.3	99.6
	CIN1+	481	0	470	15	100.0	73.4	100.0
	CIN2+	481	0	470	9	100.0	51.3	100.0

Immunogenicity

Up to 76 months following first vaccination in Study HPV-001, 98.6% or more of the vaccinees remained seropositive for both HPV-16 and HPV-18 (as measured by ELISA). Geometric mean titre (GMT) levels for both HPV-16 and HPV-18 showed a plateau during Study HPV-007 at approximately one log below the peak response level observed at Month 7 (in Study HPV-001) without substantial evidence of further decline between Month 18 and the last time intervals evaluated (Months 69-74 and 75-76). An overview of the seropositivity rates and GMTs for anti-HPV-16 and anti-HPV-18 antibodies at each time point is shown in Table 5 and Table 6 respectively.

Table 5: Seropositivity rates and GMTs for anti-HPV-16 IgG antibodies (ATP cohort for immunogenicity)

				≥ 8 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-16 IgG	Vaccine	PRE	301	18	6.0	3.6	9.3	4.3	4.2	4.4	<8.0	30.0
		PIII(M7)	301	301	100	98.8	100	4197.5	3766.1	4678.3	65.0	34561.0
		PIII(M12)	302	302	100	98.8	100	1241.0	1094.7	1406.8	70.0	25655.0
		PIII(M18)	300	299	99.7	98.2	100	737.8	651.0	836.2	<8.0	10228.0
		[M25-M32]	71	70	98.6	92.4	100	670.4	489.2	918.8	<8.0	9900.0
		[M33-M38]	172	171	99.4	96.8	100	454.7	381.7	541.6	<8.0	4974.0
		[M39-M44]	126	126	100	97.1	100	567.8	475.9	677.4	46.0	5264.0
		[M45-M50]	190	190	100	98.1	100	399.4	340.6	468.5	29.0	4562.0
		[M51-M56]	100	100	100	96.4	100	622.8	506.1	766.5	74.0	6137.0
		[M57-M62]	179	179	100	98.0	100	426.7	362.0	503.0	29.0	5479.0
		[M63-M68]	103	103	100	96.5	100	542.3	439.7	668.7	64.0	5659.0
		[M69-M74]	178	177	99.4	96.9	100	394.3	332.0	468.4	<8.0	4233.0
		[M75-M76]	52	52	100	93.2	100	463.6	360.8	595.5	89.0	4707.0
	Control	PRE	5	0	0.0	0.0	52.2	4.0	4.0	4.0	<8.0	<8.0
		PIII(M7)	5	1	20.0	0.5	71.6	4.9	2.8	8.6	<8.0	11.0
		PIII(M12)	5	0	0.0	0.0	52.2	4.0	4.0	4.0	<8.0	<8.0
		PIII(M18)	5	0	0.0	0.0	52.2	4.0	4.0	4.0	<8.0	<8.0
		[M25-M32]	54	5	9.3	3.1	20.3	4.4	4.0	4.7	<8.0	13.0
		[M33-M38]	131	14	10.7	6.0	17.3	4.9	4.3	5.4	<8.0	405.0
		[M39-M44]	85	10	11.8	5.8	20.6	4.8	4.3	5.5	<8.0	125.0
		[M45-M50]	142	16	11.3	6.6	17.7	4.8	4.3	5.3	<8.0	151.0
		[M51-M56]	69	9	13.0	6.1	23.3	5.1	4.2	6.1	<8.0	677.0
		[M57-M62]	131	26	19.8	13.4	27.7	5.5	4.8	6.2	<8.0	181.0
		[M63-M68]	67	10	14.9	7.4	25.7	4.8	4.3	5.3	<8.0	21.0
		[M69-M74]	130	13	10.0	5.4	16.5	4.8	4.4	5.4	<8.0	72.0
		[M75-M76]	35	4	11.4	3.2	26.7	4.6	4.0	5.3	<8.0	17.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminium hydroxide (DVLP018A)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
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
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)
[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)
[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)
[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)
[M75-M76] = Post Dose III (75<=Month<=76)

Table 6: Seropositivity rates and GMTs for anti-HPV-18 IgG antibodies (ATP cohort for immunogenicity)

				≥ 7 EL. U/mL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV-18 IgG	Vaccine	PRE	301	30	10.0	6.8	13.9	3.9	3.8	4.1	<7.0	33.0
		PIII(M7)	300	300	100	98.8	100	3358.0	3041.8	3707.0	107.0	45888.0
		PIII(M12)	302	302	100	98.8	100	995.3	888.5	1115.0	91.0	30401.0
		PIII(M18)	300	299	99.7	98.2	100	591.9	524.7	667.8	<7.0	7518.0
		[M25-M32]	71	70	98.6	92.4	100	596.9	439.6	810.5	<7.0	12988.0
		[M33-M38]	172	171	99.4	96.8	100	378.6	320.0	447.9	<7.0	3711.0
		[M39-M44]	127	126	99.2	95.7	100	435.1	351.1	539.0	<7.0	11173.0
		[M45-M50]	190	190	100	98.1	100	297.5	254.4	348.0	22.0	5649.0
		[M51-M56]	100	100	100	96.4	100	454.9	370.8	558.1	23.0	8272.0
		[M57-M62]	179	179	100	98.0	100	322.5	274.9	378.4	23.0	4775.0
		[M63-M68]	103	103	100	96.5	100	359.9	295.0	439.2	24.0	6130.0
		[M69-M74]	178	177	99.4	96.9	100	305.3	258.1	361.1	<7.0	3415.0
		[M75-M76]	52	52	100	93.2	100	279.8	218.0	359.1	55.0	2408.0
	Control	PRE	5	0	0.0	0.0	52.2	3.5	3.5	3.5	<7.0	<7.0
		PIII(M7)	5	1	20.0	0.5	71.6	4.1	2.6	6.5	<7.0	8.0
		PIII(M12)	5	0	0.0	0.0	52.2	3.5	3.5	3.5	<7.0	<7.0
		PIII(M18)	5	0	0.0	0.0	52.2	3.5	3.5	3.5	<7.0	<7.0
		[M25-M32]	54	4	7.4	2.1	17.9	3.9	3.5	4.3	<7.0	35.0
		[M33-M38]	131	16	12.2	7.1	19.1	4.1	3.8	4.5	<7.0	56.0
		[M39-M44]	87	15	17.2	10.0	26.8	4.6	4.0	5.4	<7.0	341.0
		[M45-M50]	142	19	13.4	8.3	20.1	4.2	3.8	4.5	<7.0	58.0
		[M51-M56]	68	13	19.1	10.6	30.5	4.7	3.8	5.6	<7.0	561.0
		[M57-M62]	131	16	12.2	7.1	19.1	4.2	3.8	4.5	<7.0	44.0
		[M63-M68]	66	10	15.2	7.5	26.1	4.3	3.7	4.9	<7.0	52.0
		[M69-M74]	131	19	14.5	9.0	21.7	4.5	4.0	5.0	<7.0	121.0
		[M75-M76]	35	5	14.3	4.8	30.3	4.3	3.6	5.2	<7.0	27.0

Vaccine = HPV-16/18 L1/AS04 (DVLP017A)
Control = Aluminium hydroxide (DVLP018A)
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
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
PRE = Prevaccination
PIII(M7) = Post Dose III (Month 7); PIII(M12) = Post Dose III (Month 12); PIII(M18) = Post Dose III (Month 18)
[M25-M32] = Post Dose III (25<=Month<=32); [M33-M38] = Post Dose III (33<=Month<=38)
[M39-M44] = Post Dose III (39<=Month<=44); [M45-M50] = Post Dose III (45<=Month<=50)
[M51-M56] = Post Dose III (51<=Month<=56); [M57-M62] = Post Dose III (57<=Month<=62)
[M63-M68] = Post Dose III (63<=Month<=68); [M69-M74] = Post Dose III (69<=Month<=74)
[M75-M76] = Post Dose III (75<=Month<=76)

A similar pattern of functional antibody responses was observed for HPV-16 and HPV-18 using the V5/J4 inhibition tests and pseudovirion neutralizing assay. Anti-HPV-16 and anti-HPV-18 antibody titres were well above the natural infection level at each time point considered. To further assess the immune response over time, a *post-hoc* analysis of the ATP kinetic cohort was performed. The antibody kinetics for both HPV-16 and HPV-18 antibodies are in line with other HPV studies (that is, peak antibody levels at Month 7 followed by gradual decline of antibodies until Month 18). Similar to other studies, the decrease of the antibody levels from Month 18 onwards is less pronounced than the decrease observed between previous time intervals. The immunogenicity results obtained in the Total cohort were consistent with those obtained in the ATP cohort.

In summary, up to 76 months following first vaccination in Study HPV-001, 98.6% or more of the vaccinees remained seropositive for both HPV-16 and HPV-18 as measured by ELISA. For both antigens, the GMTs reached a plateau during the HPV-007 study at approximately one log below the peak response level observed at Month 7 in the HPV-001 study without substantial evidence of further decline between Month 18 and Month 76 post vaccination. This suggested that the proposed vaccine is highly immunogenic

Study HPV- 008

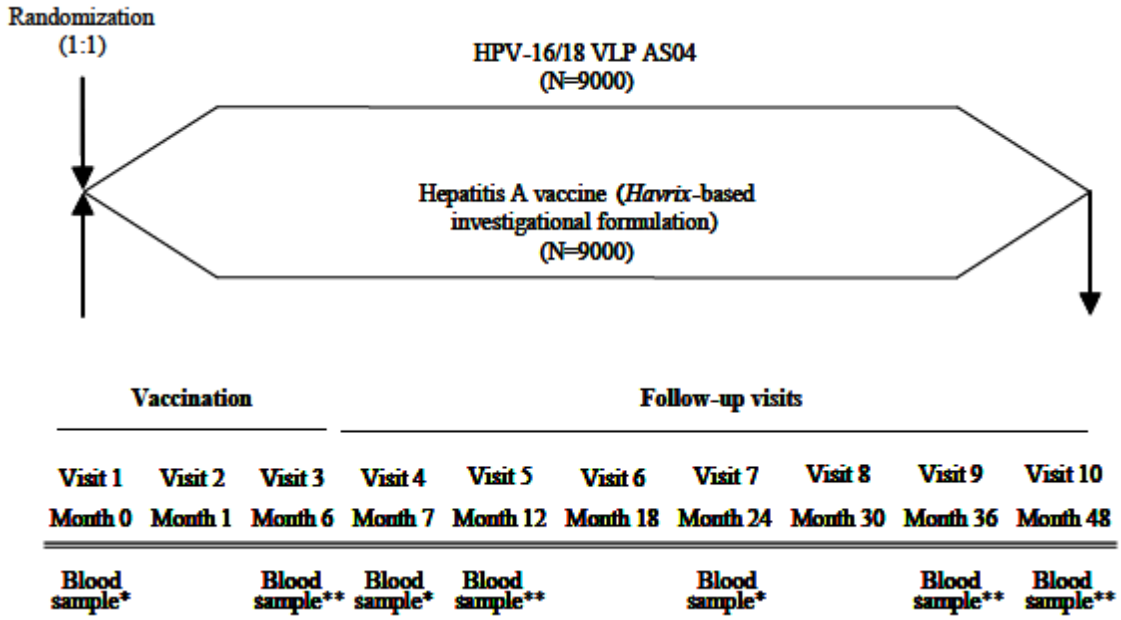
Study HPV-008 was a large, Phase III, double-blind, randomised, controlled, multi-centre study designed to evaluate the efficacy, immunogenicity and safety of the HPV-16/18 L1 AS04 vaccine in healthy females from 15 to 25 years of age. The study was appropriately controlled and included two parallel groups receiving either HPV-16/18 L1 AS04 (*Cervarix*) or a Hepatitis A control (randomised 1:1). The study was conducted in accordance with good clinical practice (GCP) and all regulatory requirements.

Methods

Study design

An overview of the study design is shown in Figure 3.

Figure 3: Overview of study design



N= planned number of subjects. * All subjects had blood drawn at these time points. ** A subset of subjects from selected study sites (immunogenicity subset) had additional blood samples taken at these time points.

Vaccination schedule

Three doses of vaccine or control (active) according to a 0, 1 and 6-month schedule. The target enrollment was 18 000 women aged 15 to 25 years from Asia Pacific, Europe, Latin America and North America. Data was collected by remote data entry (RDE).

- Approximately 48 months of follow-up was planned for all subjects with ten scheduled visits per subject at Months 0, 1, 6, 7, 12, 18, 24, 30, 36 and 48.
- A subset of subjects from selected study sites (that is, Safety Diary Card subset: N≥4000, at least 1000 per region) completed safety diary cards to record solicited (Days 0-6) and unsolicited symptoms (Days 0-29) after each vaccination. Serious

adverse events (SAEs), pregnancies and their outcomes, NOCD, medically significant conditions and sexually transmitted diseases were collected throughout the trial in all subjects.

- Blood samples were drawn from all subjects at Months 0, 7 and 24. In a subset of subjects from selected study sites (that is, Immunogenicity subset: N≥2000, at least 500 per region), additional blood samples were taken at Months 6, 12, 36 and 48*.
- Gynecological examination was performed in all subjects at Months 0, 12, 24, 36 and 48*.
- Cervical liquid-based cytology (LBC) samples were collected in all subjects at Months 0, 6, 12, 18, 24, 30, 36 and 48* for:
    - HPV DNA typing by PCR, performed on LBC samples collected at Months 0, 6, 12, 18, 24, 30, 36 and 48*.
    - Cytopathological examination, performed on LBC samples collected at Months 0, 12, 24, 36 and 48* using the Bethesda system[1] of cervical cytology reporting.
    - *Chlamydia trachomatis* and *Neisseria gonorrhea* testing, performed on LBC samples collected at Months 0, 12, 24, 36 and 48*.
- Colposcopic referral and/or repeat cytology were performed according to appropriate clinical management algorithms.
- All CIN endpoints were confirmed by an expert histopathology review panel that was blinded to vaccine status, HPV DNA status before biopsy, and cytology reports.
- Behavioural questionnaires were completed by interview at Months 1, 12, 24, 36 and 48*.

*some subjects are still active in the study and have not had their Month 48 visit.

Randomization of subjects

The enrolment was performed to try to distribute the population across the four regions (Asia Pacific, Europe, Latin America and North America). At first vaccination (Day 0), the treatment allocation was performed at the investigator sites using a central randomization system on the Internet (SBIR). If the subject was eligible, the investigator entered the subject number and her age range (15-17, 18-21 or 22-25 years). In return, the system allocated a unique treatment number using a minimization algorithm taking into account the study site and the subject age range. The algorithm ensured a balanced distribution between the six randomization groups (vaccine lots) within the stratification factors (study sites and age ranges).

Study Analyses:

- An event-driven interim analysis was performed when at least 23 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the Total Vaccinated cohort for efficacy 1 (TVC-1) These data were reported in a separate interim clinical study report dated March 2007.
- An event-driven final analysis was performed when at least 36 cases of CIN2+ associated with HPV-16 or HPV-18 infection were detected in the ATP cohort for efficacy, including at least 15 cases of CIN2+ associated with HPV-18 infection.

The efficacy objectives were assessed at the final analysis post Dose 3 in women who were DNA negative for the corresponding HPV type at Months 0 and 6. These data are presented in the final clinical study report. The endpoints assessed at the interim analysis were assessed again at the final analysis with higher power to evaluate the endpoints.

[1] The Bethesda System for reporting cervical or vaginal cytologic diagnoses was introduced in 1988 (and has been revised since) to establish uniform terminology and standardize diagnostic reports. In addition, it introduced a standardized approach for reporting if an individual specimen is adequate for evaluation.

Activities at study completion:

After the database was frozen for final analysis, there was unblinding and cross-over immunization of both treatment and control recipients offered the HPV vaccine or (GSK) licensed *Havrix*[2] vaccine, as appropriate.

Analysis issues

Before the interim analysis, potential study conduct and data integrity issues were identified at one site in the USA. The site was closed and subjects from the site were unblinded with respect to their treatment allocation and HPV DNA results. Follow-up gynecological care and crossover vaccination were provided outside of the study. All subjects from this site (N=21) were excluded from all analyses.

- **Primary objective**
  - To demonstrate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR). The principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample
- **Secondary objectives**
  - The safety and immunogenicity of HPV-16/18 L1 AS04 was evaluated as secondary endpoints. For all serostratified secondary and exploratory efficacy analyses, the principal analysis was performed on subjects who were seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample. Secondary objectives are presented in the order defined in the protocol.

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

    Histopathological
  - To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed CIN2+ associated with the following oncogenic HPV types (or combination of types) detected within the cervical lesion in the cervical tissue specimen (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.
  - To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed CIN1+ associated with HPV-16 or HPV-18 detected within the cervical lesion (by PCR), overall and stratified according to initial (Month 0) HPV-16 or 18 serostatus (by ELISA).
  - To evaluate efficacy of the candidate vaccine compared with control in the prevention of histopathologically-confirmed CIN1+ associated with the following oncogenic HPV types detected within the cervical lesion (by PCR): HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, post Dose 3 in women negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type.

[2] Havrix is a vaccine used to prevent hepatitis A infection.

Immunogenicity

- To evaluate vaccine immunogenicity in a subset of subjects from selected study sites (immunogenicity subset: N ≥2000, at least 500 per region), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus.
- To evaluate immune correlates of protection against persistent infections (6- and 12-month definition) with HPV-16 or 18 and CIN2+ associated with HPV-16 or 18 cervical infection (by PCR) post Dose 3 using Month 7 and Month 24 immunogenicity evaluations.

Safety

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

At the time the study protocol for HPV-008 was being developed there were limited data in women 15-25 years of age with respect to CIN2+ lesions and their association with specific HPV genotypes. Therefore, the protocol-specified analysis of the primary endpoint did not take into account the possible detection of multiple oncogenic HPV types (multiple infections) in a single lesion. In addition, the PCR methodology used in the study was highly sensitive and allowed the detection of a broad range of oncogenic and non-oncogenic HPV types, including types not contained in the vaccine. The inclusion of women into the study who had prevalent oncogenic HPV infections at baseline, coupled with sensitive PCR methodology, allowed the detection of HPV DNA resulting from incident infections acquired during the study. To take these multiple infections into account during the interim analysis, the sponsor performed a *post-hoc* analysis of histopathological outcomes using a HPV type assignment algorithm (HPV TAA), also referred to as the clinical case assignment. For cases with more than one HPV type detected in the lesion, the association between the cervical lesion and the HPV type was based not only on the detection of HPV DNA in the lesion, but also on the presence of HPV types in the two immediately preceding cytology samples. As a result of this, the final analysis included the HPV TAA algorithm as an exploratory endpoint for the final analysis of HPV-008. In the final analysis, the TAA was performed, not only for clinical endpoints associated with HPV-16 and HPV-18, but also for the next seven most prevalent oncogenic types, that is, HPV-31, -33, -35, -45, -51, -58 and -68.

In summary, the final analysis was triggered when at least 36 cases of CIN2+ associated with HPV-16/18 infection, and at least 15 cases of CIN2+ associated with HPV-18, were detected in the ATP cohort for efficacy. Endpoints evaluated at the interim analysis were assessed again at the final analysis, with alpha adjustment and increased power. The mean follow-up at final analysis was approximately 39 months (34.9 months for the ATP cohort for efficacy, starting at Dose 3 and 39.4 months in the TVC-1 for efficacy, starting at Dose 1). For the analyses of safety based on the Total Vaccinated Cohort (TVC), the mean follow-up time was 40.8 months (starting at Dose 1). Some participants continue to be followed (to the total of 48 months) under the supervision of an Independent Data Monitoring Committee (IDMC). To maintain the study blind, the interim and final analyses were performed by an external statistician on a frozen, validated database.

Enrolment

Healthy females were enrolled after their eligibility criteria were checked at study entry. Exclusion criteria aimed to prevent the administration of study vaccines to individuals with medical conditions that could interfere with the vaccine induced immune response, that is, to those at risk of possible adverse reactions to the vaccine; those in whom previous exposure to the vaccine antigens through vaccination, disease or known exposure would prevent interpretation of the results and those who were pregnant or at risk of becoming pregnant during the vaccination period. Women in the study were vaccinated without pre-screening for HPV and were included regardless of their baseline cytology and HPV serological and DNA status. The overall population studied therefore included women previously uninfected with

HPV, and women previously or currently infected with HPV. This population can be considered as broadly representative of the sexually active female adolescent and young adult population.

The principal analyses were performed on subjects who were HPV DNA negative for all types (by PCR) and seronegative for HPV-16/18 (by ELISA) for the corresponding HPV type at baseline. These analyses are indicative of the prophylactic efficacy of the vaccine in the target population of young females prior to sexual debut. In order to evaluate the possible need for serological screening prior to vaccination, additional analyses were performed in HPV DNA negative subjects who were seropositive for the corresponding HPV type at baseline, or in HPV DNA negative subjects regardless of their initial serostatus. Vaccine efficacy in HPV DNA positive subjects was an exploratory endpoint.

Methods to Evaluate Efficacy/Immunogenicity

At both the interim and final analysis of Study HPV-008, the presence of HPV type specific DNA in cervical specimens and biopsy samples was evaluated using a generic (SPF10) PCR. Blood samples were taken from all subjects at Months 0, 7 and 24. There was an additional immunogenicity subset of subjects that consisted of ≥2,000 subjects (at least 500 subjects per region) from study sites selected to collect additional blood samples at Months 6, 12, 36 and 48. Serological assays were performed using standardized validated procedures with adequate controls. A high correlation in antibody titres between the ELISA and the pseudovirion neutralizing assay (PBNA) has been demonstrated for both HPV-16 and HPV-18 for up to 6.4 years after the primary vaccination course (Dessy, 2008[3]).

Statistical Methods

Vaccine efficacy (VE) for all endpoints was calculated using a conditional exact method (primary analysis). This methodology takes into account the follow-up time of subjects in each group. Confirmatory analysis of adjusted vaccine efficacy using Cox regression evaluated the possible effect of different covariates (age, region, number of sexual partners, hormonal contraception, occurrence of another lower genital tract infection and smoking) on estimated vaccine efficacy. There was also an exploratory analysis of all histopathological outcomes using the HPV TAA. For cases with more than one HPV type detected in the lesion, the association between the cervical lesion and the HPV type was based also on the presence of HPV types in the two immediately preceding cytology samples. The antibody titres associated with naturally acquired HPV-16 or HPV-18 infection and successful immunological clearance of infection were evaluated at baseline in the Total Vaccinated Cohort. The calculation of GMTs was performed on subjects who were seropositive for HPV-16 or HPV-18 at Month 0 and who were HPV DNA negative for the antigen considered (that is, who had successfully cleared the infection and mounted an immune response). Subjects who had cleared HPV-16 infection had GMTs of 29.8 EL.U/ml [28.6; 31.0]. Subjects who had cleared HPV-18 infection had GMTs of 22.6 EL.U/ml [21.6; 23.6]. The ATP cohort for analysis of efficacy included all evaluable subjects who had received three doses and who had a normal or low-grade cytology at Month 0. Subjects had to be negative for HPV DNA at Month 0 and Month 6 for the corresponding HPV type in the analysis. Follow-up time for a subject started the day after Dose 3.

Total cohort for efficacy 1 (TVC-1)

At the final analysis, TVC-1 for efficacy included all vaccinated subjects who had received at least one dose of study vaccine and who had a normal or low-grade cytology at Month 0. Subjects with high-grade abnormal or missing cytology at baseline were excluded from this

[3] Dessy FJ, Giannini SL, Bougelet CA, *et al*. Correlation between direct ELISA, single epitope-based inhibition ELISA and pseudovirion-based neutralisation assay for measuring anti-HPV-16 and anti-HPV-18 antibody response after vaccination with the AS04-adjuvanted HPV-16/18 cervical cancer vaccine. *Hum Vaccin*. 2008; 4: 425-34.

analysis. Follow-up time for a subject started the day after Dose 1. At the final analysis, TVC-1 was the primary cohort for all efficacy endpoints evaluated in HPV DNA positive women at Month 0.

Supplementary analyses of efficacy

Three additional supplementary analyses were performed at final analysis: Total Vaccinated Cohort for efficacy 2 (TVC-2) and sub-analyses in naïve subjects from the ATP and TVC cohorts (ATP-naïve and TVC-naïve, respectively). The Total Vaccinated Cohort for efficacy 2 (TVC-2) was the same as TVC-1 for efficacy, except that subjects with abnormal cytology at baseline were excluded. TVC-2 included all vaccinated subjects who had received at least one dose and who had a normal cytology at Month 0. The ATP-naïve cohort was performed on all evaluable subjects who were negative for all High Risk (HR) HPV types (by DNA) at Month 0 and Month 6, seronegative for HPV-16 and HPV-18 at Month 0 and who had a normal cytology at Month 0. The follow-up time for a subject started the day after Dose 3. The TVC-naïve analysis included all vaccinated subjects who had received at least one dose and who had a normal cytology at Month 0. Subjects had to be seronegative for both HPV-16 and HPV-18 and HPV DNA negative for all HR HPV at Month 0. Follow-up time for a subject started the day after Dose 1. The analyses in naïve subjects were only performed on primary, secondary and selected exploratory endpoints. Results from the TVC-2, ATP-naïve and TVC-naïve analyses for efficacy are not discussed in detail in this submission.

According to protocol (ATP) cohort for immunogenicity

The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity. This cohort was based on a subset of subjects from study sites selected to collect blood samples at Months 0, 6, 7, 12, 24, 36 and 48 and included subjects with at least one ELISA result after completion of the full three-dose primary vaccination course (N=1,933: 1,035 in the vaccine group and 898 in the control group). Subjects who acquired either HPV-16 or HPV-18 infection during the trial (which could influence HPV antibody levels) were excluded from the ATP cohort for immunogenicity. Due to the high efficacy of HPV-16/18 L1 AS04, more subjects in the HAV group (N=2,117) developed HPV-16/18 infections than in the HPV group (N=1,119) and were eliminated from the ATP cohort for immunogenicity. Subjects who had developed HPV-16/18 infections were included in the Total Vaccinated cohort for immunogenicity but not this subset. Analysis of antibody kinetics was performed on subjects in the ATP cohort for immunogenicity who had an ELISA/PBNA (neutralising antibodies) result available at all timepoints. The primary analysis of safety was performed on the Total Vaccinated Cohort (TVC) and included all vaccinated subjects who had received at least one dose and had safety data available.

Results

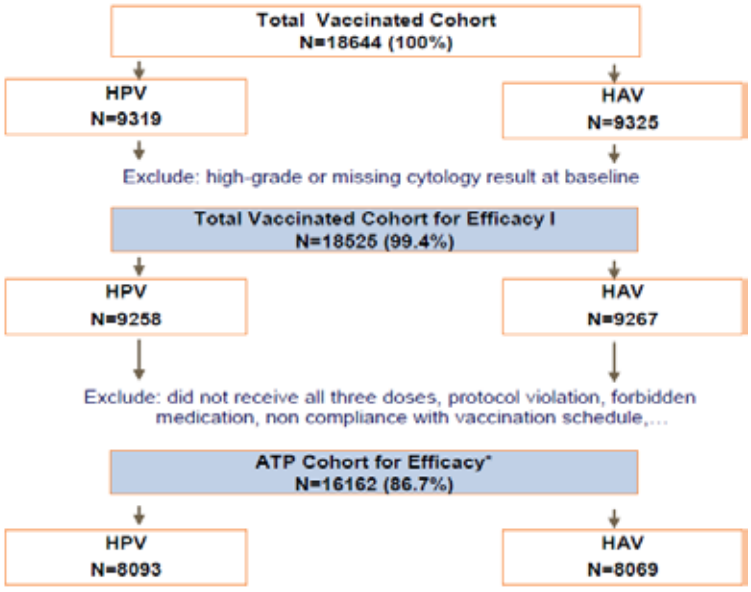
Study participants

A total of 18,729 subjects were enrolled and of these 18,665 were vaccinated. The study was conducted in 14 countries (Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippines, Spain, Taiwan, Thailand, UK and USA). There were no major differences with respect to age, racial distribution, height and weight between groups in the study. At baseline, approximately 26% of women had evidence of a current or prior HPV-16/18 infection and less than 1% of women were HPV DNA positive (+) for both HPV-16 and HPV-18. Subjects initially infected with a specific HPV type were not eligible for the efficacy assessment of that type.

Sample size

A summary of the number of subjects included in the Total Vaccinated Cohort (TVC) for Safety, the Total Vaccinated Cohort for efficacy 1 (TVC-1) and the According-to-protocol Cohort for efficacy (ATP Cohort for efficacy) is provided in Figure 4.

Figure 4: Number of Subjects in Key Cohorts of Study HPV-008



*primary cohort for efficacy analyses

Efficacy Results

Primary endpoint:-

- **CIN2+ associated with HPV-16/18 Subjects HPV DNA negative and seronegative at baseline**

A high level of vaccine efficacy against CIN2+ lesions associated with HPV-16/18 was observed in both the ATP and TVC-1 cohorts for efficacy for both the protocol-specified analysis of efficacy and the HPV TAA exploratory analysis (Table 7).

In the ATP cohort, VE was 92.9% [96.1% CI: 79.9, 98.3]; p<0.0001. Statistically significant vaccine efficacy was also observed against CIN2+ associated with both HPV-16 (VE=95.7% [96.1% CI: 82.9, 99.6]; p<0.0001) and HPV-18 (VE=86.7% [96.1% CI: 39.7, 98.7]; p = 0.0013). Based on the exploratory analysis using the HPV TAA, vaccine efficacy against CIN2+ related to HPV-16/18 was statistically significant with a slightly higher point estimate and higher lower limit of the confidence interval (VE=98.1% [96.1% CI: 88.4, 100]; p<0.0001) than in the pre-specified analysis. Analyses of the TVC-1 cohort for efficacy confirm this high level of efficacy. The TVC-1 cohort for efficacy included protocol violators and women who had not received three doses of vaccine. Some of these women could have developed lesions from infections acquired prior to completion of the vaccine course. Compared with the ATP cohort for efficacy there was one additional case of CIN2+ in the HPV group and 35 additional cases in the HAV group. In the TVC-1 cohort for efficacy, vaccine efficacy against CIN2+ associated with HPV-16/18 was 94.5% [96.1% CI: 86.2, 98.4], p<0.0001. Statistically significant vaccine efficacy was also observed against CIN2+ associated with HPV-16 (VE=95.9% [96.1% confidence interval (CI) 87.0, 99.3], p<0.0001) and HPV-18 (VE=91.6% [96.1% CI: 64.6, 99.2], p<0.0001). Based on the exploratory analysis using the HPV TAA, vaccine efficacy against CIN2+ related to HPV-16/18 was statistically significant with a slightly higher point estimate and higher lower limit of the confidence interval (VE=97.7% [96.1% CI: 91.0, 99.8], p<0.0001) than in the pre-specified analysis.

Table 7: Summary of vaccine efficacy against CIN2+ and CIN3+ associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP and TVC-1)

Endpoint (cohort)	HPV		HAV		VE			
	N	n	N	n	%	LL	UL	P-value
CIN2+ Associated with HPV-16 and/or HPV-18								
CIN2+ (ATP)	7344	4	7312	56	92.9	79.9	98.3	<0.0001
CIN2+ (ATP TAA)	*7344*	*1*	*7312*	*53*	*98.1*	*88.4*	*100.0*	*<0.0001*
CIN2+ (TVC-1)	8040	5	8080	91	94.5	86.2	98.4	<0.0001
CIN2+ (TVC-1 TAA)	*8040*	*2*	*8080*	*87*	*97.7*	*91.0*	*99.8*	*<0.0001*
CIN3+ Associated with HPV-16 and/or HPV-18								
CIN 3+ (ATP)	*7344*	*2*	*7312*	*10*	*80.0*	*0.3*	*98.1*	*0.0221*
CIN3+ (ATP TAA)	*7344*	*0*	*7312*	*8*	*100*	*36.4*	*100*	*0.0038*
CIN3+ (TVC-1)	*8040*	*2*	*8080*	*22*	*90.9*	*60.8*	*99.1*	*<0.0001*
CIN3+ (TVC-1 TAA)	*8040*	*0*	*8080*	*20*	*100*	*78.1*	*100*	*<0.0001*
CIN2+ Associated with HPV-16								
CIN2+ (ATP)	6303	2	6165	46	95.7	82.9	99.6	<0.0001
CIN2+ (ATP TAA)	*6303*	*0*	*6165*	*45*	*100.0*	*91.0*	*100.0*	*<0.0001*
CIN2+ (TVC-1)	6921	3	6923	73	95.9	87.0	99.3	<0.0001
CIN2+ (TVC-1 TAA)	*6921*	*1*	*6923*	*71*	*98.6*	*91.5*	*100.0*	*<0.0001*
CIN3+ Associated with HPV-16								
CIN 3+ (ATP)	*6303*	*2*	*6165*	*6*	*67.2*	*-97.1*	*97.2*	*0.1749*
CIN3+ (ATP TAA)	*6303*	*0*	*6165*	*6*	*100*	*8.8*	*100*	*0.0146*
CIN3+ (TVC-1)	*6921*	*2*	*6923*	*16*	*87.5*	*43.8*	*98.8*	*0.0013*
CIN3+ (TVC-1 TAA)	*6921*	*0*	*6923*	*16*	*100*	*72.1*	*100*	*<0.0001*
CIN2+ Associated with HPV-18								
CIN2+ (ATP)	6794	2	6746	15	86.7	39.7	98.7	0.0013
CIN2+ (ATP TAA)	6794	1	6746	13	92.3	45.7	99.9	0.0009
CIN2+ (TVC-1)	7455	2	7480	24	91.6	64.6	99.2	<0.0001
CIN2+ (TVC-1 TAA)	7455	1	7480	22	95.4	70.1	99.9	<0.0001
CIN3+ Associated with HPV-18								
CIN 3+ (ATP)	*6794*	*0*	*6746*	*5*	*100*	*-19.3*	*100*	*0.0307*
CIN3+ (ATP TAA)	*6794*	*0*	*6746*	*3*	*100*	*-170.5*	*100*	*0.1236*
CIN3+ (TVC-1)	*7455*	*0*	*7480*	*7*	*100*	*24.2*	*100*	*0.0156*
CIN3+ (TVC-1 TAA)	*7455*	*0*	*7480*	*5*	*100*	*-20.3*	*100*	*0.0625*

Note: Exploratory analyses are presented in *italics*
ATP = ATP cohort for efficacy (protocol-defined analyses)
TVC-1 = TVC cohort for efficacy (protocol-defined analyses)
TAA = HPV type assignment algorithm (exploratory analyses)
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
CIN2+ = CIN2, CIN3, AIS or ICC (primary endpoint)
CIN3+ = CIN3, AIS or ICC (exploratory analysis)
Subjects with an event were HPV DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

The exploratory evaluation of vaccine efficacy against CIN3+ associated with HPV-16/18 was statistically significant at 80.0% [96.1% CI: 0.3, 98.1], p=0.0221 with two cases in the HPV group compared to ten cases in the HAV group (Table 7). When the HPV TAA was applied to this analysis, vaccine efficacy against CIN3+ related to HPV-16/18 was also statistically significant at 100% [96.1% CI: 36.4, 100], p=0.0038 with no cases in the HPV group compared to eight cases in the HAV group in the ATP cohort for efficacy. In subjects who were HPV DNA negative and HPV seronegative at baseline, vaccine efficacy against CIN3+ associated with HPV-16/18 was 90.9% [96.1% CI: 60.8, 99.9], p<0.0001 with 2 cases in the HPV group versus 22 cases in the HAV group in TVC-1. When the HPV TAA was applied to this analysis, vaccine efficacy against

CIN3+ related to HPV-16/18 was also statistically significant at 100% [96.1% CI: 78.1, 100], p<0.0001 with no cases in the HPV group compared to 20 cases in the HAV group in TVC-1.

- **Subjects HPV DNA negative, regardless of HPV-16/18 serostatus at baseline**

At enrolment, 13.9% of subjects were HPV DNA negative and seropositive for HPV-16 and 10.6% of subjects were HPV DNA negative and seropositive for HPV-18. In subjects who were HPV DNA negative at baseline regardless of initial serostatus, vaccine efficacy against CIN2+ associated with HPV-16/18 was still statistically significant (VE=90.8% [96.1% CI: 78.1, 96.9], p<0.0001 in the ATP cohort (Table 8) and VE=92.3% [96.1% CI 83.8, 96.9], p<0.0001 in the TVC-1 (Table 9). Based on the exploratory analysis using the HPV TAA, vaccine efficacy against CIN2+ related to HPV-16/18 was also statistically significant in the ATP cohort (VE=98.4% [96.1% CI: 90.0, 100], p<0.0001; Table 8) and in the TVC-1 (VE=97.0% [96.1% CI: 90.5, 99.4], p<0.0001, Table 9). Vaccine efficacy against CIN3+ associated with HPV-16/18 in this population was also statistically significant (VE=84.6% [96.1% CI: 28.2, 98.5], p=0.0041) with 2 cases in the HPV group versus 13 cases in the HAV group in the ATP cohort. Based on the exploratory analysis using the HPV TAA, vaccine efficacy against CIN3+ related to HPV-16/18 was 100% ([96.1% CI: 57.0, 100], p=0.0005) in the ATP cohort. In conclusion, in the supplementary analysis of the primary endpoint which included subjects without considering their initial HPV-16/18 serostatus, vaccine efficacy against HPV-16/18 remained high in both the ATP and TVC-1 cohorts for efficacy.

- **Subjects HPV DNA negative and seropositive for corresponding HPV type at baseline**

There were fewer cases of histopathological and virological endpoints associated with HPV16/18 in the small population of subjects who were HPV DNA negative but seropositive for the corresponding type at baseline. In the ATP cohort for efficacy, there were eight cases of CIN2+, all associated with HPV-16 (two cases in the HPV group and six cases in the HAV group, Table 8). In TVC-1 there were 13 cases of the CIN2+, all associated with HPV-16 (three in the HPV group and ten cases in the HAV group, Table 9). These results were not statistically significant. This result is limited by the low number of cases of CIN2+ associated with HPV-16/18.

Summary of virological and histopathological endpoints associated with HPV-16/18

A summary of vaccine efficacy against histopathological, cytological and virological endpoints associated with HPV-16/18 evaluated in HPV DNA negative and seronegative subjects in the ATP cohort for efficacy and TVC-1 is presented in Table 8 and Table 9, respectively.

Table 8: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (ATP cohort for efficacy)

Endpoint	HPV		HAV		VE			
	N	n	N	n	%	LL	UL	P-value
Associated with HPV-16 and/or HPV-18								
Incident infection	*7346*	*263*	*7320*	*1074*	*76.7*	*73.2*	*79.9*	*<0.0001*
Persistent infection (6-month)	7177	32	7122	497	93.8	91.0	95.9	<0.0001
Persistent infection (12-month)	7035	21	6984	233	91.2	85.9	94.8	<0.0001
Any cytological abnormality (ASC-US+)	*7340*	*51*	*7312*	*434*	*88.5*	*84.4*	*91.7*	*<0.0001*
CIN2+	7344	4	7312	56	92.9	79.9	98.3	*<0.0001*
CIN2+ (TAA)	*7344*	*1*	*7312*	*53*	*98.1*	*88.4*	*100.0*	*<0.0001*
CIN1+	7344	8	7312	96	91.7	82.4	96.7	<0.0001
CIN1+ (TAA)	*7344*	*2*	*7312*	*90*	*97.8*	*91.4*	*99.8*	*<0.0001*
VIN/VaIN1+	*7344*	*2*	*7312*	*10*	*80.0*	*0.3*	*98.1*	*0.0221*
CIN3+	*7344*	*2*	*7312*	*10*	*80.0*	*0.3*	*98.1*	*0.0221*
CIN3+ (TAA)	7344	0	7312	8	100	36.4	100	0.0038
Associated with HPV-16								
Incident infection	*6304*	*139*	*6172*	*687*	*80.9*	*76.8*	*84.4*	*<0.0001*
Persistent infection (6-month)	6163	23	6018	345	93.7	90.1	96.1	<0.0001
Persistent infection (12-month)	6052	18	5903	175	90.1	83.5	94.4	<0.0001
Any cytological abnormality (ASC-US+)	*6299*	*33*	*6165*	*279*	*88.6*	*83.3*	*92.4*	*<0.0001*
CIN2+	6303	2	6165	46	95.7	82.9	99.6	*<0.0001*
CIN2+ (TAA)	*6303*	*0*	*6165*	*45*	*100.0*	*91.0*	*100.0*	*<0.0001*
CIN1+	6303	5	6165	70	93.0	82.2	97.9	<0.0001
CIN1+ (TAA)	*6303*	*1*	*6165*	*66*	*98.5*	*91.0*	*100.0*	*<0.0001*
VIN/VaIN1+	*6303*	*2*	*6165*	*6*	*67.2*	*-97.0*	*97.2*	*0.1749*
CIN3+	*6303*	*2*	*6165*	*6*	*67.2*	*-97.1*	*97.2*	*0.1749*
CIN3+ (TAA)	6303	0	6165	6	100	8.8	100	0.0146
Associated with HPV-18								
Incident infection	*6796*	*134*	*6751*	*509*	*74.4*	*68.7*	*79.3*	*<0.0001*
Persistent infection (6-month)	6642	9	6567	188	95.3	90.7	98.0	<0.0001
Persistent infection (12-month)	6508	3	6440	70	95.8	86.6	99.2	<0.0001
Any cytological abnormality (ASC-US+)	*6790*	*20*	*6746*	*204*	*90.3*	*84.4*	*94.4*	*<0.0001*
CIN2+	6794	2	6746	15	86.7	39.7	98.7	0.0013
CIN2+ (TAA)	*6794*	*1*	*6746*	*13*	*92.3*	*45.7*	*99.9*	*0.0009*
CIN1+	6794	3	6746	31	90.4	67.7	98.3	<0.0001
CIN1+ (TAA)	*6794*	*1*	*6746*	*29*	*96.6*	*78.1*	*99.9*	*<0.0001*
VIN/VaIN1+	*6794*	*0*	*6746*	*4*	*100*	*-67.0*	*100*	*0.0616*
CIN3+	*6794*	*0*	*6746*	*5*	*100*	*-19.3*	*100*	*0.0307*
CIN3+ (TAA)	6794	0	6746	3	100	-170.5	100	0.1236

Note: Exploratory endpoints are shown in *italics*. *CIN3+ data is based on an exploratory sub-analysis of CIN2+ data.*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
TAA = HPV type assignment algorithm
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
CIN3+ = CIN3, AIS or ICC
Subjects DNA negative at Month 0 and Month 6 and seronegative at Month 0 for HPV-16 or HPV-18
Follow-up period starts at day after Dose 3
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Table 9: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-16/18 in HPV DNA negative and seronegative subjects at baseline (TVC-1)

Endpoint	HPV		HAV		VE			
	N	n	N	n	%	LL	UL	P-value
Associated with HPV-16 and/or HPV-18								
Incident infection	*8225*	*368*	*8252*	*1374*	*74.6*	*71.3*	*77.5*	*<0.0001*
Persistent infection (6-month)	7941	71	7964	671	89.8	86.8	92.2	<0.0001
Persistent infection (12-month)	7812	53	7823	347	85.0	79.7	89.2	<0.0001
Any cytological abnormality (ASC-US+)	*8040*	*79*	*8080*	*560*	*86.1*	*82.2*	*89.3*	*<0.0001*
CIN2+	8040	5	8080	91	94.5	86.2	98.4	<0.0001
CIN2+ (TAA)	*8040*	*2*	*8080*	*87*	*97.7*	*91.0*	*99.8*	*<0.0001*
CIN1+	8040	11	8080	135	91.8	84.5	96.2	<0.0001
CIN1+ (TAA)	*8040*	*5*	*8080*	*128*	*96.1*	*90.3*	*98.8*	*<0.0001*
VIN/VaIN1+	*8040*	*2*	*8080*	*12*	*83.2*	*20.2*	*98.4*	*0.0129*
CIN3+	*8040*	*2*	*8080*	*22*	*90.9*	*60.8*	*99.1*	*<0.0001*
CIN3+ (TAA)	8040	0	8080	20	100	78.1	100	<0.0001
Associated with HPV-16								
Incident infection	*7073*	*203*	*7074*	*909*	*78.7*	*74.9*	*81.9*	*<0.0001*
Persistent infection (6-month)	6846	45	6834	481	91.0	87.5	93.6	<0.0001
Persistent infection (12-month)	6738	36	6723	260	86.4	80.4	90.9	<0.0001
Any cytological abnormality (ASC-US+)	*6921*	*52*	*6923*	*376*	*86.4*	*81.5*	*90.2*	*<0.0001*
CIN2+	6921	3	6923	73	95.9	87.0	99.3	<0.0001
CIN2+ (TAA)	*6921*	*1*	*6923*	*71*	*98.6*	*91.5*	*100.0*	*<0.0001*
CIN1+	6921	7	6923	100	93.0	84.6	97.4	<0.0001
CIN1+ (TAA)	*6921*	*3*	*6923*	*94*	*96.8*	*90.0*	*99.4*	*<0.0001*
VIN/VaIN1+	*6921*	*2*	*6923*	*7*	*71.4*	*-60.9*	*97.5*	*0.1795*
CIN3+	*6921*	*2*	*6923*	*16*	*87.5*	*43.8*	*98.8*	*0.0013*
CIN3+ (TAA)	6921	0	6923	16	100	72.1	100	<0.0001
Associated with HPV-18								
Incident infection	*7623*	*180*	*7641*	*641*	*72.5*	*67.3*	*77.1*	*<0.0001*
Persistent infection (6-month)	7363	26	7373	243	89.4	83.8	93.4	<0.0001
Persistent infection (12-month)	6508	3	6440	70	83.7	72.0	91.2	<0.0001
Any cytological abnormality (ASC-US+)	*7455*	*30*	*7480*	*253*	*88.2*	*82.5*	*92.4*	*<0.0001*
CIN2+	7455	2	7480	24	91.6	64.6	99.2	<0.0001
CIN2+ (TAA)	*7455*	*1*	*7480*	*22*	*95.4*	*70.1*	*99.9*	*<0.0001*
CIN1+	7455	4	7480	42	90.5	72.6	97.7	<0.0001
CIN1+ (TAA)	*7455*	*2*	*7480*	*40*	*95.0*	*79.7*	*99.5*	*<0.0001*
VIN/VaIN1+	*7455*	*0*	*7480*	*5*	*100*	*-20.3*	*100*	*0.0625*
CIN3+	*7455*	*0*	*7480*	*7*	*100*	*24.2*	*100*	*0.0156*
CIN3+ (TAA)	7455	0	7480	5	100	-20.3	100	0.0625

Note: Exploratory endpoints are shown in *italics*. *CIN3+ data is based on an exploratory sub-analysis of CIN2+ data.*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
N = number of subjects included in each group; n = number of subjects reporting at least one event in each group

TAA = HPV type assignment algorithm, ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC; CIN1+ = CIN1, CIN2, CIN3, AIS or ICC; CIN2+ = CIN2, CIN3, AIS or ICC; CIN3+ = CIN3, AIS or ICC. Subjects with an event were DNA negative and seronegative for the corresponding HPV type at Month 0. Follow-up period starts at day after Dose 3. VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits. P-value = Two-sided Fisher Exact test.

In the principal analysis of subjects who were HPV DNA negative and seronegative at baseline, statistically significant vaccine efficacy was observed for histopathological and cytological endpoints associated with HPV-16/18, in both the ATP cohort for efficacy and TVC-1 (Table 8 and Table 9, respectively). Statistically significant vaccine efficacy was also observed for CIN2+, CIN1+ and ASC-US+ associated with HPV-16 and with HPV 18. The exploratory analysis of CIN3+ associated with HPV-16/18 was statistically significant in the ATP cohort for efficacy

(Table 8). For CIN3+, there were only two cases associated with HPV-16 in the HPV group versus six in the HAV group and only five cases associated with HPV-18, all of which were in the HAV group (Table 8). However, when there are more cases identified, as in the TVC-1, statistically significant vaccine efficacy against CIN3+ associated with both HPV-16 and with HPV-18 was demonstrated. Furthermore, statistically significant vaccine efficacy against all virological endpoints (6-month persistent infection and 12-month persistent infection as secondary endpoints; incident infection as an exploratory endpoint) with HPV 16/18 was also observed in both the ATP cohort for efficacy and the TVC-1 (Table 8 and Table 9, respectively). Statistically significant vaccine efficacy was also observed for all HPV-16 and HPV-18 virological endpoints.

Some exploratory analyses, such as the combined endpoint VIN/VaIN1+ associated with HPV-16 or with HPV-18, were not statistically significant due to the low numbers reported in both groups (two cases of VIN1+/VaIN1+ associated with HPV-16 in the HPV group compared to six cases in the HAV group and only four cases of VIN1+/VaIN1+ associated with HPV-18, all of which were in the HAV group) (Table 8). Similar results were observed in TVC-1 (Table 9).

Overview of vaccine efficacy in HPV DNA negative subjects, stratified by serostatus at baseline

An overview of vaccine efficacy against all histopathological, cytological and virological endpoints evaluated in this population is presented for the ATP cohort for efficacy and TVC-1 in Tables 10 and 11, respectively.

When initial serostatus was not taken into account, vaccine efficacy against all efficacy endpoints associated with HPV-16/18 remained high in both the ATP cohort for efficacy and in the TVC-1. In subjects that were HPV DNA negative but seropositive for the corresponding type at baseline, statistically significant vaccine efficacy was observed for all virological endpoints and ASC-US+ in both the ATP cohort for efficacy and in the TVC-1 (see Table 10 and Table 11, respectively). CIN1+ was not statistically significant in the ATP cohort for efficacy but was statistically significant in the TVC-1. Vaccine efficacy against CIN2+ associated with HPV-16/18 or VIN/VaIN associated with HPV-16/18 was not statistically significant in either of the two cohorts (ATP or TVC-1) for efficacy (once again, very low numbers were used in this analysis).

Table 10: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-16/18 in HPV DNA negative subjects, regardless of serostatus and in seropositives at baseline (ATP cohort for efficacy)

	HPV		HAV		VE			
Endpoint	**N**	**n**	**N**	**n**	**%**	**LL**	**UL**	**P-value**
Associated with HPV-16/18 in HPV DNA negative subjects at baseline, regardless of initial serostatus								
Incident infection	*7815*	*324*	*7775*	*1207*	*74.6*	*71.1*	*77.7*	*<0.0001*
Persistent infection (6-month)	7619	41	7556	549	92.8	90.0	95.0	<0.0001
Persistent infection (12-month)	7466	23	7404	258	91.3	86.4	94.7	<0.0001
Any cytological abnormality (ASC-US+)	*7809*	*62*	*7767*	*476*	*87.3*	*83.2*	*90.5*	*<0.0001*
VIN/VaIN1+	*7814*	*2*	*7767*	*11*	*81.9*	*11.8*	*98.3*	*0.0127*
CIN1+	7814	12	7767	111	89.3	79.9	94.8	<0.0001
CIN1+ (TAA)	*7814*	*2*	*7767*	*103*	*98.1*	*92.5*	*99.8*	*<0.0001*
CIN2+	7814	6	7767	65	90.8	78.1	96.9	<0.0001
CIN2+ (TAA)	*7814*	*1*	*7767*	*61*	*98.4*	*90.0*	*100*	*<0.0001*
CIN3+	*7814*	*2*	*7767*	*13*	*84.6*	*28.2*	*98.5*	*0.0041*
CIN3+ (TAA)	*7814*	*0*	*7767*	*11*	*100*	*57.0*	*100*	*0.0005*
Associated with HPV-16/18 in HPV DNA negative and seropositive subjects at baseline								
Incident infection	*1509*	*61*	*1551*	*133*	*53.7*	*35.8*	*66.9*	*<0.0001*
Persistent infection (6-month)	1462	9	1496	47	80.6	58.6	92.0	<0.0001
Persistent infection (12-month)	1427	2	1461	24	91.5	64.0	99.2	<0.0001
Any cytological abnormality (ASC-US+)	*1509*	*11*	*1547*	*40*	*72.0*	*42.6*	*87.6*	*<0.0001*
VIN/VaIN1+	*1510*	*0*	*1547*	*1*	*100*	*-5070.4*	*100*	*1.0000*
CIN1+	1510	4	1547	12	65.8	-18.8	92.6	0.0764
CIN1+ (TAA)	*1510*	*0*	*1547*	*10*	*100*	*50.6*	*100*	*0.0019*
CIN2+	1510	2	1547	6	65.8	-105.7	97.1	0.2887
CIN2+ (TAA)	*1510*	*0*	*1547*	*5*	*100*	*-22.9*	*100*	*0.0624*

Note: Exploratory endpoints are shown in *italics. CIN3+ data is based on an exploratory sub-analysis of CIN2+ data.*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
CIN3+ = CIN3, AIS or ICC
TAA = HPV type assignment algorithm
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits

Table 11: Summary of vaccine efficacy against histopathological and virological endpoints associated with HPV-16/18 in HPV DNA negative subjects, regardless of serostatus and in seropositives at baseline (TVC-1)

	HPV		HAV		VE			
Endpoint	**N**	**n**	**N**	**n**	**%**	**LL**	**UL**	**P-value**
Associated with HPV-16/18 in HPV DNA negative subjects at baseline, regardless of initial serostatus								
Incident infection	*8761*	*465*	*8756*	*1557*	*71.8*	*68.5*	*74.7*	*<0.0001*
Persistent infection (6-month)	8450	93	8447	752	88.1	85.1	90.7	<0.0001
Persistent infection (12-month)	8304	66	8292	391	83.5	78.3	87.7	<0.0001
Any cytological abnormality (ASC-US+)	*8562*	*99*	*8575*	*623*	*84.4*	*80.5*	*87.7*	*<0.0001*
VIN/VaIN1+	*8562*	*2*	*8575*	*14*	*85.7*	*34.1*	*98.6*	*0.0042*
CIN1+	8562	17	8575	155	89.1	81.5	94.0	<0.0001
CIN1+ (TAA)	*8562*	*7*	*8575*	*147*	*95.3*	*89.6*	*98.2*	*<0.0001*
CIN2+	8562	8	8575	104	92.3	83.8	96.9	<0.0001
CIN2+ (TAA)	*8562*	*3*	*8575*	*99*	*97.0*	*90.5*	*99.4*	*<0.0001*
CIN3+	*8562*	*2*	*8575*	*28*	*92.8*	*70.2*	*99.3*	*<0.0001*
CIN3+ (TAA)	*8562*	*0*	*8575*	*26*	*100*	*83.6*	*100*	*<0.0001*
Associated with HPV-16/18 in HPV DNA negative and seropositive subjects at baseline								
Incident infection	*1749*	*96*	*1790*	*188*	*48.2*	*32.5*	*60.4*	*<0.0001*
Persistent infection (6-month)	1667	21	1729	73	70.6	50.4	83.3	<0.0001
Persistent infection (12-month)	1630	13	1693	39	65.6	32.2	83.8	0.0004
Any cytological abnormality (ASC-US+)	*1699*	*19*	*1763*	*61*	*68.0*	*44.3*	*82.5*	*<0.0001*
VIN/VaIN1+	*1699*	*0*	*1763*	*2*	*100*	*-540.9*	*100*	*0.5000*
CIN1+	1699	6	1763	19	67.2	11.0	89.9	0.0147
CIN1+ (TAA)	*1699*	*2*	*1763*	*17*	*87.8*	*45.8*	*98.8*	*0.0007*
CIN2+	1699	3	1763	10	68.8	-28.2	95.0	0.0924
CIN2+ (TAA)	*1699*	*1*	*1763*	*9*	*88.5*	*10.8*	*99.8*	*0.0215*

Note: Exploratory endpoints are shown in *italics*. *CIN3+ data is based on an exploratory sub-analysis of CIN2+ data.*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
CIN3+ = CIN3, AIS or ICC
TAA = HPV type assignment algorithm
N = number of subjects included in each group
n = number of subjects reporting at least one event in each group
Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits

- **Overview of vaccine efficacy in subjects infected with the other vaccine type at baseline**

Vaccine efficacy in subjects who were naïve for the type considered in the analysis, but had a history of infection with the other vaccine type at baseline (that is, women who were seropositive and/or DNA positive) was statistically significant for 6-month persistent infection (VE=80.3% [96.1% CI: 66.4, 89.2] p<0.0001) and CIN2+ (VE=81.3% [96.1% CI: 8.9, 98.2], p=0.0224). Although the confidence interval around vaccine efficacy was wider for CIN2+ than for 6-month persistent infection, it appears that the administration of the vaccine to a subject who has a genital infection with one HPV vaccine type does not affect the prophylactic efficacy of the vaccine against the other HPV vaccine type. As the proportion of women with simultaneous infection with HPV-16 and HPV-18 was low, this finding indicates that the majority of the female population could benefit from the protection provided by the vaccine against HPV-16/18 infections.

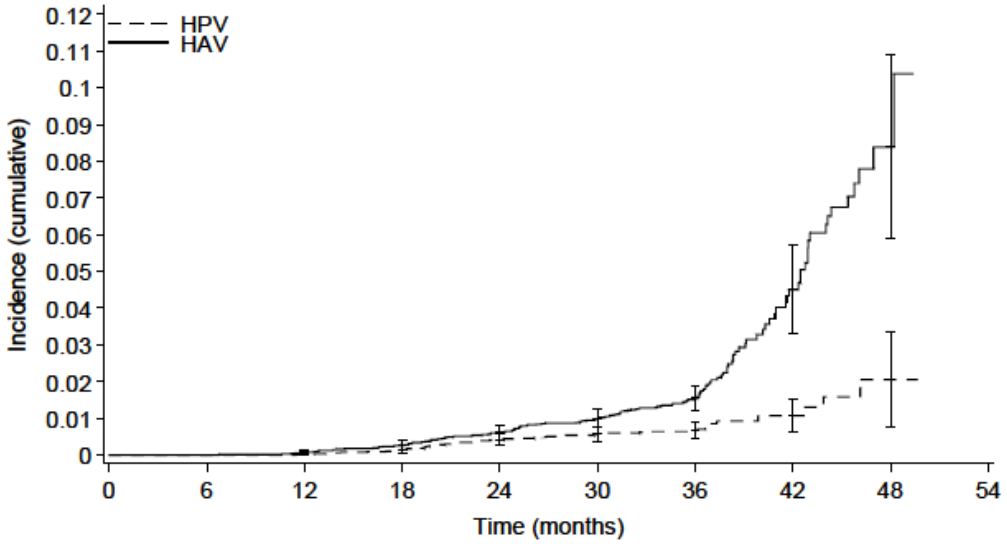
- **Overview of overall vaccine efficacy, irrespective of the HPV type in the lesion and stratified according to subjects baseline HPV DNA status**

An exploratory assessment of overall vaccine efficacy was performed based on the total number of cases irrespective of the HPV type present in the lesion (by PCR) and stratified by the subject's baseline HPV DNA status, regardless of initial serostatus (Table 12).

High levels of prophylactic vaccine efficacy were seen overall for CIN2+, CIN1+ and ASC-US+ in subjects who were DNA negative for oncogenic HPV types or all HPV types at baseline in the TVC-1 (Table 12) as well as in the ATP cohort for efficacy. In TVC-1, the overall vaccine efficacy against all CIN2+, irrespective of the HPV DNA type detected in the lesion and irrespective of the subject's baseline HPV DNA and serostatus, was statistically significant (VE=30.9% [91.6% CI: 16.4, 43.0], p<0.0001).

Figure 5 presents the cumulative incidence curve for CIN2+, irrespective of HPV DNA type in the lesion, in subjects who were DNA negative for all oncogenic HPV types, regardless of initial serostatus, in TVC-1.

Figure 5: Cumulative incidence curve for CIN2+ irrespective of HPV type in the lesion for subjects DNA negative for all oncogenic types at baseline (TVC-1)



Number at risk

HPV	6893	6885	6777	6639	6321	5949	2723	481	58	0
HAV	6962	6950	6814	6648	6363	5989	2733	552	59	0

Number of cases (cumulative)

HPV	0	0	1	10	28	36	42	48	51	51
HAV	0	0	5	18	41	64	93	126	141	142

In the TVC-naïve cohort, vaccine efficacy against all CIN2+, irrespective of HPV DNA results was 70.2% ([91.6% CI: 54.7, 80.9], p<0.0001) and against all CIN1+, irrespective of HPV DNA results was 50.1% ([91.6% CI: 35.9, 61.4], p<0.0001).

Table 12: Overview of overall vaccine efficacy irrespective of HPV DNA in the lesion, stratified by HPV DNA status at baseline, regardless of initial serostatus (TVC-1)

Endpoint	HPV		HAV		Vaccine Efficacy			
	n	N	n	N	%	LL	UL	P-value
In subjects irrespective of HPV DNA at baseline, regardless of serostatus								
CIN2+	204	8610	296	8630	30.9	16.4	43.0	<0.0001
CIN1+	422	8610	549	8630	23.0	11.8	32.8	<0.0001
ASC-US+	1951	8610	2185	8630	11.2	5.3	16.8	<0.0001
VIN/VaIN1+	39	8610	53	8630	26.1	-16.3	53.5	0.1739
In subjects negative for oncogenic HPV types at baseline, regardless of serostatus								
CIN2+	51	6893	142	6962	63.8	49.0	74.7	<0.0001
CIN1+	157	6893	278	6962	43.1	29.9	54.0	<0.0001
ASC-US+	1173	6893	1397	6962	16.0	8.8	22.6	<0.0001
VIN/VaIN1+	18	6893	34	6962	46.5	-0.3	72.5	0.0363
In subjects negative for all HPV types at baseline, regardless of serostatus								
CIN2+	47	6565	132	6651	64.0	48.6	75.3	<0.0001
CIN1+	136	6565	259	6651	47.0	33.9	57.8	<0.0001
ASC-US+	1058	6565	1298	6651	18.3	11.0	25.1	<0.0001
VIN/VaIN1+	18	6565	31	6651	41.2	-11.7	70.0	0.0852

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
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
P-value=Two-sided Fisher Exact test

Vaccine efficacy against endpoints associated with oncogenic HPV types (cross-protection)

In Study HPV-008, vaccine efficacy was evaluated against 12 non-vaccine oncogenic HPV types (HPV-31, -33, -35, -39, -45, -51, -56, -58, -59, -66 and -68). At final analysis, additional data were available for cross-protection against other oncogenic HPV types, which confirmed and strengthened the results observed at the interim analysis.

· **Cross-protective efficacy against oncogenic HPV types**

A summary of vaccine efficacy against histopathological and virological endpoints associated with all high-risk (oncogenic) HPV types (HR-HPV), or for all high-risk (oncogenic) HPV types excluding HPV-16/18 (HRW-HPV), in HPV DNA negative subjects at baseline is provided for the ATP cohort for efficacy in Table 12 and for TVC-1 in Table 13. The analyses of HRW-HPV may include lesions with multiple HPV types; although these were associated with another oncogenic type besides HPV-16/18 they may also contain HPV-16 or HPV-18 within the lesion as these two types are ignored in the case definition. Therefore, the analysis of vaccine efficacy for histopathological endpoints with HRW-HPV may still be partially confounded by the presence of HPV-16 and/or HPV-18. Consistently high levels of efficacy were observed for incident infection, 6-month and 12-month persistent infection, ASC-US+, CIN1+ and CIN2+, in both the ATP cohort for efficacy and the TVC-1 (Tables 13 and 14).

Table 13: Summary of vaccine efficacy against virological and histopathological endpoints associated with oncogenic HPV types in HPV DNA negative subjects at baseline (ATP cohort for efficacy)

	HPV		HAV		VE			
Endpoint	**N**	**n**	**N**	**n**	**%**	**LL**	**UL**	**P-value**
Associated with HR-HPV								
Incident infection with HR – HPV types	*7864*	*2746*	*7861*	*3119*	*14.5*	*9.7*	*19.0*	*<0.0001*
Any cytological abnormality (ASC-US+)	*7858*	*953*	*7853*	*1212*	*22.1*	*14.8*	*28.9*	*<0.0001*
Persistent infection (6-month)	7665	1271	7640	1647	25.0	18.9	30.6	<0.0001
Persistent infection (12-month)	*7509*	*585*	*7488*	*803*	*28.4*	*19.8*	*36.1*	*<0.0001*
CIN1+	7863	151	7853	279	45.9	33.1	56.4	<0.0001
CIN1+ (TAA)	*7863*	*134*	*7853*	*262*	*48.9*	*36.1*	*59.3*	*<0.0001*
CIN2+	7863	54	7853	142	61.9	46.7	73.2	<0.0001
CIN2+ (TAA)	*7863*	*46*	*7853*	*131*	*64.8*	*49.6*	*75.9*	*<0.0001*
VIN/VaIN1+	*7863*	*14*	*7853*	*32*	*56.1*	*12.7*	*79.2*	*0.0078*
Associated with HRW-HPV								
Incident infection	*7864*	*2624*	*7861*	*2846*	*9.0*	*3.7*	*13.9*	*0.0002*
Any cytological abnormality (ASC-US+)	*7858*	*931*	*7853*	*1094*	*15.3*	*7.0*	*22.8*	*0.0001*
Persistent infection (6-month)	7665	1247	7640	1406	12.1	4.7	19.0	0.0005
Persistent infection (12-month)	*7509*	*567*	*7488*	*643*	*12.1*	*0.9*	*22.1*	*0.0209*
CIN1+	7863	146	7853	233	37.3	21.7	49.9	<0.0001
CIN1+ (TAA)	*7863*	*133*	*7853*	*215*	*38.0*	*21.9*	*51.1*	*<0.0001*
CIN2+	7863	50	7853	109	54.0	34.0	68.4	<0.0001
CIN2+ (TAA)	*7863*	*45*	*7853*	*99*	*54.4*	*33.3*	*69.3*	*<0.0001*
VIN/VaIN1+	*7863*	*13*	*7853*	*25*	*47.8*	*-9.6*	*76.4*	*0.0528*

Note: Exploratory endpoints are shown in *italics*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
TAA = HPV type assignment algorithm (exploratory analysis)
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6
HRW-HPV = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
Follow-up period starts at day after Dose 3
VE (%) = Vaccine Efficacy (Conditional Method)
LL, UL = 96.1% Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Table 14: Summary table of vaccine efficacy against virological and histopathological endpoints associated with oncogenic HPV types in HPV DNA negative subjects at baseline (TVC-1)

	HPV		HAV		VE			
Endpoint	**N**	**n**	**N**	**n**	**%**	**LL**	**UL**	**P-value**
Associated with HR-HPV								
Incident infection	*8803*	*3389*	*8802*	*3842*	*14.5*	*10.2*	*18.6*	*<0.0001*
Any cytological abnormality (ASC-US+) s	*8602*	*1214*	*8621*	*1520*	*21.0*	*14.4*	*27.1*	*<0.0001*
Persistent infection (6-month)	8488	1649	8492	2117	24.7	19.3	29.6	<0.0001
Persistent infection (12-month)	*8340*	*849*	*8336*	*1138*	*27.0*	*19.8*	*33.6*	*<0.0001*
CIN1+	8602	212	8621	364	41.8	30.3	51.6	<0.0001
CIN1+ (TAA)	*8602*	*201*	*8621*	*351*	*42.8*	*31.1*	*52.6*	*<0.0001*
CIN2+	8602	81	8621	192	57.8	44.2	68.3	<0.0001
CIN2+ (TAA)	*8602*	*75*	*8621*	*184*	*59.2*	*45.6*	*69.7*	*<0.0001*
VIN/VaIN1+	*8602*	*20*	*8621*	*36*	*44.3*	*-1.7*	*70.4*	*0.0437*
Associated with HRW-HPV								
Incident infection	*8803*	*3246*	*8802*	*3512*	*8.8*	*4.0*	*13.3*	*<0.0001*
Any cytological abnormality (ASC-US+)	*8602*	*1182*	*8621*	*1368*	*14.0*	*6.6*	*20.8*	*<0.0001*
Persistent infection (6-month)	8488	1598	8492	1812	12.9	6.5	18.9	<0.0001
Persistent infection (12-month)	*8340*	*796*	*8336*	*903*	*12.4*	*3.0*	*20.8*	*0.0062*
CIN1+	8602	203	8621	303	33.0	18.9	44.7	<0.0001
CIN1+ (TAA)	*8602*	*196*	*8621*	*286*	*31.4*	*16.6*	*43.7*	*<0.0001*
CIN2+	8602	76	8621	141	46.0	27.0	60.3	<0.0001
CIN2+ (TAA)	*8602*	*73*	*8621*	*132*	*44.6*	*24.5*	*59.6*	*<0.0001*
VIN/VaIN1+	*8602*	*19*	*8621*	*28*	*31.9*	*-30.3*	*65.2*	*0.2423*

Note: Exploratory endpoints are shown in *italics*
HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
N = number of subjects included in each group; n = number of subjects reporting at least one event in each group
TAA = HPV type assignment algorithm (exploratory analysis)
ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
Subjects with an event were DNA negative for the corresponding HPV type at Month 0
HPV-HRW = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18
HPV-HR = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
Follow-up period starts at day after Dose 1
VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits
P-value = Two-sided Fisher Exact test

Vaccine efficacy against 6 month persistent infection and CIN2+ associated with non-vaccine HPV types in the ATP cohort for efficacy is presented in Table 15.

Table 15: Summary table of vaccine efficacy against individual non-vaccine oncogenic HPV types for 6-month persistent infection and CIN2+ (ATP cohort for efficacy)

ATP cohort[1]						
HPV type	6 month persistent infection			CIN 2+		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n	n		n	n	
HPV-16 related types[2]						
HPV-31	46	215	78.7% (70.2;85.2)	2	25	92.0% (66.0;99.2)
HPV-33	67	123	45.7% (25.1;60.9)	12	25	51.9% (<0;78.9)
HPV-35	56	46	-22.2% (<0;20.4)	1	6	83.3% (<0;99.7)
HPV-52	314	339	7.8% (<0;21.8)	12	14	14.3% (<0;65.4)
HPV-58	144	147	1.8% (<0;23.4)	6	17	64.5% (1.5;89.2)
HPV-18 related types[2]						
HPV-39	147	149	1.0% (<0;22.7)	3	10	69.8% (<0;95.2)
HPV-45[3]	23	94	75.7% (60.4;85.7)	0	4	100 (<0;100)
HPV-59	97	111	12.4% (<0;34.9)	1	4	74.9% (<0;99.6)
HPV-68	138	134	-3.1% (<0;20.3)	5	11	54.4% (<0;88.4)
Other types[2]						
HPV-51	304	354	14.5% (<0;27.4)	10	27	62.9% (18.0;84.7)
HPV-56	182	174	-5.0% (<0;16.1)	4	10	59.9% (<0;91.5)
HPV-66	168	178	5.7% (<0;24.9)	4	10	60.0% (<0;91.6)

n= number of cases

[1] 3 doses of vaccine, DNA negative for the corresponding HPV type in the analysis at month 0 and month 6

[2] types are listed in numerical order and not according to epidemiological data

[3] the number of CIN2+ cases associated with HPV-45 on which the estimate of vaccine efficacy was based was limited

The most prevalent HPV types associated with cervical cancer after HPV-16 and 18 are HPV-31, HPV-33, HPV-45 and HPV-51, which together account for an additional 12.2% of cervical cancers other than those caused by HPV-16 and HPV-18 (Bosch, 2008[4]). Statistically significant vaccine efficacy was observed for the main histopathological and virological endpoints associated with HPV-31 and most endpoints associated with HPV- 33, HPV 45, and HPV-51 (Tables 13, 14 and 15). Statistically significant vaccine efficacy was demonstrated for all major efficacy endpoints for HPV-31 (6-month and 12-month persistent infections, CIN1+ and CIN2+) in both the ATP cohort for efficacy and TVC-1. Statistically significant vaccine efficacy was also observed for incident infection and ASC-US+ in the ATP cohort for efficacy. In HPV DNA negative subjects, vaccine efficacy against CIN2+ associated with HPV-31 was 92% ([96.1% CI: 66.0, 99.2], p<0.0001) in the ATP cohort for efficacy. Cross-protection against HPV-45 was observed for all endpoints evaluated, except for CIN2+ which had fewer cases than the other endpoints, in both the ATP cohort for efficacy and TVC-1. Statistically significant vaccine efficacy was demonstrated for HPV-51 against 12- month persistent infection and CIN2+ in the ATP cohort for efficacy and against all key efficacy endpoints (6-month and 12-month persistent infections, CIN1+ and CIN2+) in TVC-1. In addition, there was some evidence of cross-protection for HPV-35, HPV-58 and HPV- 68 but these data were not consistent across all endpoints (Tables 16-18).

[4] Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de SS, Bruni L, Tortolero-Luna G, Kjaer SK, Munoz N. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine*. 2008; 26 Suppl 10: K1-16.

Table 16: Summary of vaccine efficacy against virological endpoints associated with specific oncogenic HPV types in HPV DNA negative subjects (ATP cohort for efficacy and TVC-1)

ATP cohort for efficacy										
	6-month persistent infection					12-month persistent infection				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**46/215**	**78.7**	**70.2**	**85.2**	**<0.0001**	**21/102**	**79.4**	**66.1**	**88.1**	**<0.0001**
HPV-33	**67/123**	**45.7**	**25.1**	**60.9**	**<0.0001**	31/50	38.0	-1.4	62.6	0.0344
HPV-35	56/46	-22.2	-88.5	20.4	0.3714	28/16	-75.8	-260.5	10.9	0.0957
HPV-45	**23/94**	**75.7**	**60.4**	**85.7**	**<0.0001**	**10/27**	**63.0**	**18.4**	**84.7**	**0.0049**
HPV-51	304/354	14.5	-0.8	27.4	0.0418	**102/139**	**26.8**	**3.5**	**44.6**	**0.0161**
HPV-58	144/147	1.8	-26.0	23.4	0.8592	64/56	-14.9	-70.7	22.5	0.5213
HPV-68	138/134	-3.1	-33.4	20.3	0.8545	46/47	1.9	-53.8	37.5	0.9175

TVC-1										
	6-month persistent infection					12-month persistent infection				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**94/283**	**66.9**	**57.6**	**74.4**	**<0.0001**	**52/138**	**62.3**	**46.9**	**73.6**	**<0.0001**
HPV-33	**96/166**	**42.2**	**24.3**	**56.1**	**<0.0001**	**48/76**	**36.8**	**6.3**	**57.8**	**0.0146**
HPV-35	77/67	-15.4	-65.4	19.3	0.4041	39/24	-63.1	-191.8	6.8	0.0594
HPV-45	**35/123**	**71.6**	**57.6**	**81.5**	**<0.0001**	**19/43**	**55.8**	**20.4**	**76.4**	**0.0022**
HPV-51	**401/475**	**15.8**	**3.0**	**27.0**	**0.0112**	**150/204**	**26.6**	**7.9**	**41.6**	**0.0037**
HPV-58	182/184	0.5	-24.1	20.3	0.9579	86/74	-17.0	-64.6	16.6	0.3413
HPV-68	185/188	1.4	-22.8	20.8	0.9166	70/72	2.5	-39.8	32.1	0.9329

* n=number of subjects reporting at least one event in each group (HPV group/HAV group). Note: Only oncogenic HPV types with at least one statistically significant result are shown. Those results shown in bold were statistically significant. Subjects with an event were HPV DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1. VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits. P-value = Two-sided Fisher Exact test

Table 17: Summary of vaccine efficacy against histopathological endpoints associated with specific oncogenic HPV types in HPV DNA negative subjects (ATP cohort for efficacy and TVC-1)

ATP cohort for efficacy										
	CIN1+					CIN2+				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**6/49**	**87.7**	**70.2**	**95.9**	**<0.0001**	**2/25**	**92.0**	**66.0**	**99.2**	**<0.0001**
HPV-33	21/34	38.1	-13.0	66.9	0.0806	12/25	51.9	-2.9	78.9	0.0332
HPV-35	4/13	69.1	-5.3	93.2	0.0308	1/6	83.3	-49.1	99.7	0.0702
HPV-45	**1/12**	**91.7**	**39.3**	**99.9**	**0.0018**	0/4	100	-67.8	100	0.0619
HPV-51	42/57	26.1	-14.4	52.7	0.1316	**10/27**	**62.9**	**18.0**	**84.7**	**0.0050**
HPV-58	**11/34**	**67.5**	**32.2**	**85.8**	**0.0005**	**6/17**	**64.5**	**1.5**	**89.2**	**0.0225**
HPV-68	11/22	49.9	-11.8	79.0	0.0571	5/11	54.4	-49.8	88.4	0.1428

TVC-1										
	CIN1+					CIN2+				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**20/65**	**69.0**	**46.9**	**82.8**	**<0.0001**	**11/34**	**67.4**	**32.0**	**85.7**	**0.0008**
HPV-33	28/46	38.9	-2.3	64.2	0.0469	**16/32**	**49.8**	**2.9**	**75.2**	**0.0291**
HPV-35	**4/17**	**79.4**	**24.1**	**94.7**	**0.0072**	**1/10**	**90.0**	**24.6**	**99.8**	**0.0117**
HPV-45	**1/15**	**93.3**	**53.8**	**99.9**	**0.0005**	0/5	100	-20.2	100	0.0625
HPV-51	**48/82**	**41.4**	**13.7**	**60.6**	**0.0035**	**12/39**	**69.2**	**38.0**	**85.9**	**0.0002**
HPV-58	**21/41**	**48.4**	**8.3**	**71.9**	**0.0150**	10/20	49.6	-17.1	79.9	0.0985
HPV-68	**15/31**	**51.5**	**4.4**	**76.5**	**0.0257**	7/15	53.2	-27.6	84.7	0.1336

* n=number of subjects reporting at least one event in each group (HPV group/HAV group). Note: Only oncogenic HPV types with at least one statistically significant result are shown. Those results shown in bold were statistically significant. CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC. Subjects with an event were HPV DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1. VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits. P-value = Two-sided Fisher Exact test

Table 18 Summary of vaccine efficacy against histopathological endpoints associated with specific oncogenic HPV types in HPV DNA negative subjects (ATP cohort for efficacy and TVC-1 based on the HPV TAA).

ATP cohort for efficacy HPV TAA										
	CIN1+					CIN2+				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**6/45**	**86.6**	**67.3**	**95.6**	**<0.0001**	**2/23**	**91.3**	**62.7**	**99.1**	**<0.0001**
HPV-33	**10/29**	**65.4**	**24.5**	**85.6**	**0.0022**	**7/22**	**68.1**	**19.6**	**89.1**	**0.0051**
HPV-35	3/10	69.9	-24.0	95.2	0.0572	1/4	74.9	-178.3	99.6	0.2186
HPV-45	**1/10**	**90.0**	**24.8**	**99.8**	**0.0062**	0/4	100.0	-67.8	100.0	0.0619
HPV-51	41/53	22.4	-21.4	50.8	0.2163	**10/25**	**59.9**	**10.4**	**83.6**	**0.0112**
HPV-58	**11/32**	**65.5**	**27.4**	**85.0**	**0.0012**	6/16	62.3	-6.0	88.6	0.0345
HPV-68	10/16	37.4	-53.0	75.8	0.2468	4/8	49.9	-98.7	89.8	0.2661

TVC-1 HPV TAA										
	CIN1+					CIN2+				
Event Type	n*	%	LL	UL	P-value	n*	%	LL	UL	P-value
HPV-31	**20/60**	**66.5**	**42.1**	**81.4**	**<0.0001**	**11/31**	**64.3**	**24.5**	**84.5**	**0.0029**
HPV-33	**17/41**	**58.4**	**23.0**	**78.6**	**0.0022**	**11/29**	**61.9**	**18.8**	**83.6**	**0.0064**
HPV-35	**3/13**	**76.8**	**11.1**	**96.2**	**0.0212**	1/7	85.7	-20.2	99.8	0.0703
HPV-45	**1/13**	**92.3**	**45.3**	**99.9**	**0.0018**	0/5	100.0	-20.2	100.0	0.0625
HPV-51	**47/76**	**38.0**	**7.9**	**58.7**	**0.0110**	**12/36**	**66.6**	**32.2**	**84.8**	**0.0007**
HPV-58	**21/39**	**45.8**	**3.0**	**70.6**	**0.0271**	10/19	47.0	-24.5	79.0	0.1358
HPV-68	14/25	43.8	-16.2	74.0	0.1077	6/12	49.8	-51.7	85.5	0.2376

*

n=number of subjects reporting at least one event in each group (HPV group/HAV group). Note: Only oncogenic HPV types with at least one statistically significant result are shown. Those results shown in bold were statistically significant. HPV TAA = HPV type assignment algorithm CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC. Subjects with an event were HPV DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type in the ATP cohort for efficacy, and DNA negative and seronegative at Month 0 in TVC-1. VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits. P-value = Two-sided Fisher Exact test

- **Reduction in local cervical therapy**

The impact of HPV-16/18 L1 AS04 on the reduction of local cervical therapy (Loop Electrosurgical Excision Procedure [LEEP], Cone, Knife and Laser) was also evaluated in subjects irrespective of the HPV DNA type detected in the lesion and irrespective of the subject's baseline HPV DNA and serostatus. Statistically significant vaccine efficacy was observed in both TVC-1 (VE=25.7% [96.1% CI: 7.6, 40.4]) and TVC (VE=24.7% [96.1% CI: 7.4, 38.9]) analyses, further confirming the similarity between these two cohorts. In the TVC-naïve cohort, vaccine efficacy to reduce local cervical therapy was 68.8% [96.1% CI: 50.0, 81.2].

- **Two dose vaccination schedule**

Most subjects in Study HPV-008 received three doses of vaccine, and only 5.2% (977 subjects) received two doses of vaccine. Approximately half of the subjects who had received two doses could not be evaluated for the exploratory analysis of vaccine efficacy, either due to lack of follow-up information or unsuitability for inclusion into the analysis. A total of 440 of the subjects who had received two doses were evaluated to assess vaccine efficacy against incident infection. Some 382 subjects were evaluated to assess vaccine efficacy against 6-month persistent infection. Vaccine efficacy against incident infection with HPV-16/18 was statistically significant (VE=72.1% [96.1% CI: 25.4, 91.3], p=0.0027). Vaccine efficacy against 6-month persistent infection with HPV-16/18 was 100% ([96.1% CI: 37.5, 100], p=0.0072).

- **Vaccine efficacy in subjects HPV DNA positive for the corresponding HPV type at baseline**

Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 in subjects who were HPV DNA positive at baseline were not statistically significant (Table 19).

Table 19: Overview of vaccine efficacy against histological lesions associated with HPV-16/18 in HPV DNA positive subjects at baseline (TVC-1).

Endpoint	HPV		HAV		Vaccine Efficacy			P-value
	N	n	N	n	%	LL	UL	
HPV DNA positive and seronegative subjects at baseline								
CIN2+	303	18	285	27	37.8	-20.9	68.8	0.1216
CIN1+	303	27	285	36	30.5	-20.9	60.5	0.1819
HPV DNA positive and seropositive subjects at baseline								
CIN2+	315	43	290	31	-32.5	-123.1	20.4	0.3205
CIN1+	315	44	290	40	-3.0	-66.0	35.9	1.0000
HPV DNA positive subjects at baseline, regardless of initial serostatus								
CIN2+	617	62	567	58	0.5	-47.7	32.9	0.9235
CIN1+	617	72	567	76	13.0	-23.8	38.9	0.3801

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CIN2+ = CIN2, CIN3, AIS or ICC
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
P-value=Two-sided Fisher Exact test

The lack of efficacy in subjects infected at baseline with the type considered in the analysis indicated the lack of therapeutic effect in the presence of active infection.

- **Vaccine effect on viral clearance of HPV-16/18**

No statistically significant differences were observed between the HPV and HAV group in terms of clearance of HPV infection present at the study start. The vaccine efficacy for clearance of HPV-16/18 infection present at study start was -3.0% ([96.1% CI: -58.4, 32.9], p=1.0000) in DNA positive and seronegative subjects at baseline. Similar results were obtained for both HPV-16 and HPV-18. There was no evidence that the vaccine prolonged HPV-16/18 infections that were already present at the time of vaccination. These results confirm those seen in the HPV-009 study where HPV vaccination did not accelerate clearance rates in HPV DNA positive women.

Immunogenicity Results

Immunogenicity evaluations by ELISA

As observed at the time of the interim analysis, three doses of HPV-16/18 L1 AS04 vaccine induced effective priming against HPV-16 and HPV-18 antigens. This was shown by high seroconversion rates and large increases in antibody GMTs between the pre- and post-dose 3 time points. When measured by ELISA, high seropositivity rates (≥99.4%) were observed for anti-HPV-16 and anti-HPV-18 antibodies up to Month 36 in the final analysis, that is, up to 30 months after completion of the full primary vaccination course. The peak response occurred at Month 7, and then GMTs for anti-HPV-16 and anti-HPV-18 antibodies gradually declined until approximately Month 24 at which a plateau level was reached. GMTs were well above levels elicited after naturally acquired infection at each timepoint post-vaccination (44.1-fold higher for HPV-16 and 24.5-fold higher for HPV-18 at Month 36). Anti-HPV-16 and anti-HPV-18 ELISA results obtained in the Total Vaccinated cohort were consistent with those obtained in the ATP cohort for immunogenicity. The anti-HPV-16/18 seropositivity status at baseline (by ELISA) was comparable between the HPV and HAV groups. Most subjects in the two groups were seronegative for both anti-HPV-16 and anti-HPV-18 antibodies at baseline (79.6% and 76.2%, respectively). The exploratory analysis of subjects vaccinated according to different schedules showed similar immune responses for subjects vaccinated according to a flexible schedule for Dose 2 (0, 2, 6-month versus 0, 1 and 6-month schedule) and subjects vaccinated according to a flexible schedule for Dose 3 (three doses administered within a period of 5 to 9 or more months).

Immunogenicity evaluations by PBNA

The analysis of anti-HPV-16 and anti-HPV-18 neutralising antibodies by PBNA, in a subset of naïve subjects (that is, DNA negative for HPV-16, 18, 31, 33 and 45 and seronegative for HPV-16 and HPV-18 at Month 0), showed a similar kinetic profile to the ELISA data described above, in terms of peak, decline and plateau.

Persistence of antibodies after vaccination

Antibody responses elicited by HPV-16/18 L1 AS04 have been evaluated up to 6.4 years (approximately 77 months) after the first dose in Studies HPV-001/HPV-007. At the final analysis of Study HPV-008, 99.4% or more of the vaccinees remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies (by ELISA) up to 30 months after completion of the three-dose vaccination course.

Study HPV- 042

GlaxoSmithKline Biologicals has conducted Study HPV-042 to evaluate the co-administration of the HPV-16/18 L1 AS04 with dTpa-IPV vaccine. Study HPV-042 was a Phase IIIb, randomised, open, multi-centre study conducted in 14 centres in France, 18 centres in Germany and three centres in Spain. In total, 751 healthy females between 10 and 18 years of age were enrolled and vaccinated. This study assessed the immunogenicity and safety of dTpa-IPV co-administered with HPV-16/18 L1 AS04 and compared it to their separate administration. The composition of the dTpa-IPV vaccine is given in Table 20. The dTpa-IPV vaccine is preservative free. By inducing an immunological response to each of the components contained in the vaccine, a booster dose of dTpa-IPV will enhance protection against diphtheria, tetanus, pertussis and poliomyelitis diseases.

Table 20: Composition of GSK Biologicals. dTpa-IPV vaccine

Ingredients	Quantity (per 0.5ml dose)
Diphtheria toxoid	≥ 2 IU (2.5 Lf)
Tetanus toxoid	≥ 20 IU (5 Lf)
Pertussis toxoid (PT)	8 µg
Filamentous haemagglutinin (FHA)	8 µg
Pertactin (PRN)	2.5 µg
Polio virus type 1	40 D antigen units
Polio virus type 2	8 D antigen units
Polio virus type 3	32 D antigen units
Aluminium (total Al 3+)	0.5 mg

IU = International Units, mL = millilitre, Lf = limit of flocculation unit, □g = microgram, D = antigen unit, mg = milligram, Poliovirus Type 1 = Mahoney strain, Type 2 = MEF-1 strain, Type 3 = Saukett strain.

Methods

The study was appropriately controlled and included two control groups: Group HPV in which no subject received dTpa-IPV vaccine and Group dTpa-IPV/HPV where dTpa-IPV and HPV-16/18 L1 AS04 vaccines were administered one month apart at separate vaccination visits, in order to fully evaluate any potential impact of co-administration. Enrolled subjects were randomised 1:1:1 to one of three study groups:

Group HPV received three doses of HPV-16/18 L1 AS04 vaccine at 0, 1 and 6 months

Group HPV + dTpa-IPV received HPV and dTpa-IPV vaccines co-administered at Month 0, followed by HPV-16/18 L1 AS04 vaccine at Months 1 and 6

Group dTpa-IPV/HPV received dTpa-IPV at Month 0, then three doses of HPV-16/18 L1 AS04 vaccine at Months 1, 2 and 7.

A schematic diagram of the study design is provided in Figure 6. The vaccines administered at each time point and the schedule used, are summarised in Table 21.

Figure 6: Study-HPV-042: Overall study design

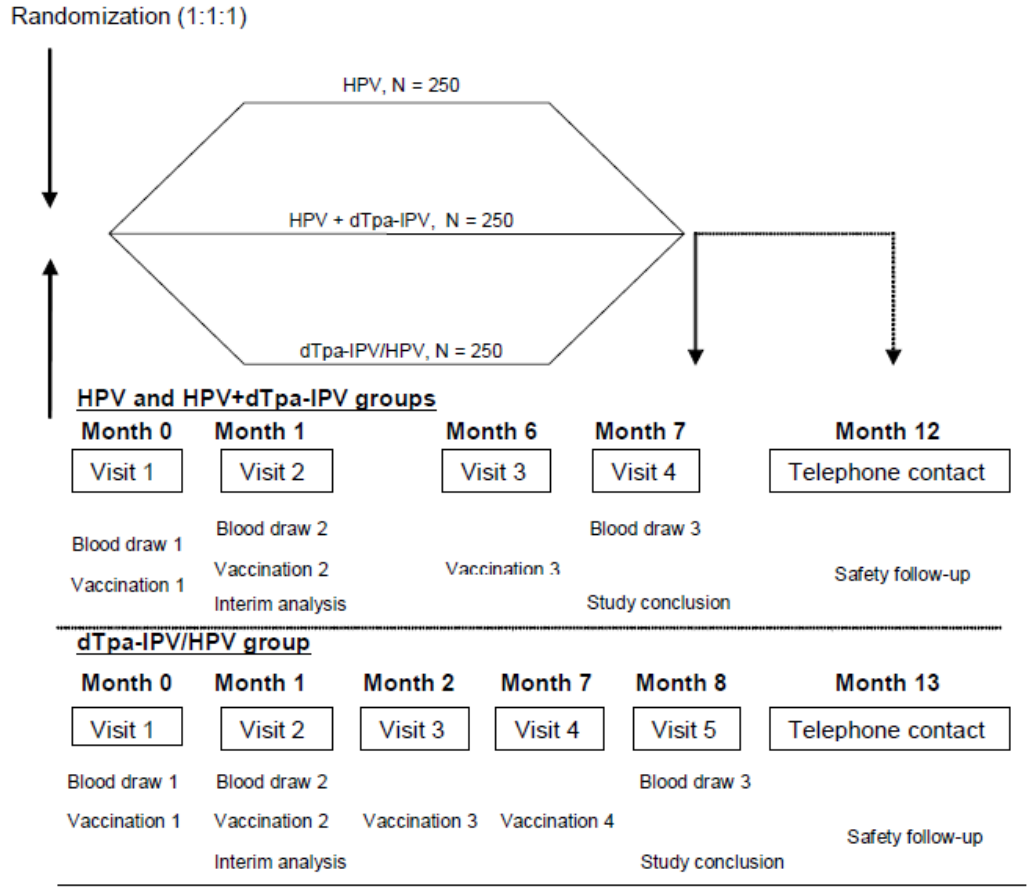


Table 21: Study HPV-042: vaccine administered and vaccination schedule

Groups	Vaccines administered and vaccination schedule				
	Month 0	Month 1	Month 2	Month 6	Month 7
HPV	HPV	HPV		HPV	
HPV+dTpa-IPV	HPV and dTpa-IPV	HPV		HPV	
dTpa-IPV/HPV	dTpa-IPV	HPV	HPV		HPV

Randomization of subjects

Approximately 750 subjects aged 10-18 years were to be enrolled in order to have a target of 711 evaluable subjects for the analysis of the primary objective at Month 1 and a target of 606 subjects at Month 7/8 for evaluation of the first secondary objective. The treatment allocation at the investigator site was performed using a central randomization system on Internet (SBIR). The randomization algorithm used a minimization procedure accounting for centre.

Primary objectives and endpoints

The primary objective of Study HPV-042 was to demonstrate non-inferiority of the dTpa-IPV immune response at Month 1 when dTpa-IPV was co-administered with HPV-16/18 L1 AS04 vaccine at Month 0 (HPV+ dTpa-IPV group) compared to when dTpa-IPV was administered

alone at Month 0 (dTpa-IPV/HPV group). This analysis was based on the measurement of appropriate antibodies to the vaccine antigens.

Secondary objectives and endpoints

The secondary non-inferiority objective of Study HPV-042 was to demonstrate non-inferiority of the HPV immune response when HPV was co-administered with dTpa-IPV at Month 0 (HPV+dTpa-IPV group) compared to when HPV was administered alone.

Study Population

Healthy females between 10-18 years were enrolled after checking eligibility criteria at study entry. Most subjects were White Caucasian of European heritage (94.9% overall). The three vaccine groups were comparable with respect to mean age and ethnicity/race of enrolled subjects.

Methods to evaluate efficacy /immunogenicity

HPV seroconversion rates were used as indicative of an immune response to vaccination with HPV-16/18 L1 AS04 vaccine. Efficacy of the dTpa-IPV vaccine was assessed by measuring the antibody response to the respective vaccine components, that is, an anti-diphtheria and anti-tetanus antibody titre of 0.01 IU/ml by *in vitro* neutralisation assay was used. In Study HPV-042, booster response rates were also used as an indicator of immunogenicity of the dTpa-IPV vaccine. No serological correlate of protection has been identified for pertussis. Serum titres of anti- PT, anti-FHA and anti-PRN antibodies were measured by ELISA. The cut-off for each ELISA was 5 El.U/ml. Booster response rates defined according to the revaccination antibody titre were also evaluated. Antibodies against Poliovirus Types 1, 2 and 3 were determined by a standard virus micro-neutralisation tests [WHO, 1993[5]]. The lowest dilution at which serum samples are tested is 1:8, from which a test is considered positive. Titres are expressed in terms of the reverse of the 50% inhibitory dose, ID_{50}. The assays and seroprotective cut-offs used are appropriate and in-line with accepted practices.

Statistical methods and endpoints

The primary cohort for the analysis of immunogenicity was based on the According to protocol (ATP) cohort. The ATP immunogenicity cohort included all subjects who met eligibility criteria, who complied with protocol-defined procedures, who had no elimination criteria during the study, and for whom data concerning immunogenicity endpoint measures were available. This cohort included non-naïve subjects at baseline.

Statistics

For each group, seroconversion/seroprotection/seropositivity rates with 95% confidence intervals (CI) and geometric mean antibody titre (GMT), with 95% CI, were calculated using standard methods. An interim analysis was conducted after all subjects had completed Visit 2 (Month 1) to evaluate the primary immunogenicity objective which was to demonstrate non-inferiority of the immune response to dTpa-IPV when co-administered with HPV-16/18 L1 AS04 compared to administration of dTpa-IPV alone.

Results from the final analysis at Month 7 and 8 (that is, study Month 7 for the HPV and HPV+dTpa-IPV groups and study Month 8 for the dTpa-IPV/HPV group) were used to assess the first secondary immunogenicity objective, which was to demonstrate non-inferiority of the response to HPV-16/18 L1 AS04 when co-administered with dTpa-IPV, compared to administration of HPV-16/18 L1 AS04 alone. The analysis of safety was conducted on the Total Vaccinated Cohort at the Month 1 interim analysis and at the final analysis at Month 7.

[5] The Immunological Basis for Immunization Series. Module 6: Poliomyelitis. Dr S. Robertson. Medical Officer Expanded Programme on Immunization* WHO (Published in 1993).

Results

Primary objective

The first pre-specified statistical criteria for non-inferiority were to show that the upper limit of the 95% CI for the group difference (dTpa-IPV/HPV group minus HPV + dTpa-IPV group) in seroprotection rates was below 5% for each of diphtheria, tetanus and polio antibodies, and the upper limit of the 95% CI for the group GMT ratio (dTpa-IPV/HPV /HPV + dTpa-IPV) was below two for antibodies against pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertactin (PRN). The results of the inferential analysis are given in Table 22. The primary objective of the study was met. Non-inferiority between co-administered and separately administered vaccine groups was demonstrated for all dTpa-IPV antigens according to the prespecified criteria.

The first secondary objective was met by showing that one month after the third HPV dose, the upper limit of the 95% CI for the group difference (HPV minus HPV + dTpa-IPV) in seroconversion rates to HPV-16 and HPV-18 was below 5%, and the upper limit of the 95% CI for the group GMT ratio (HPV/ HPV + dTpa-IPV) was below 2 for antibodies against HPV-16 and HPV-18. The results of the inferential analysis are given in Table 23. Non-inferiority between co-administered and separately administered vaccine groups was demonstrated for all HPV antigens according to the pre-specified criteria.

Table 22: Differences in seroprotection rates and geometric mean titres (GMT) ratios one month after booster vaccination with dTpa-IPV (Month 1), with 95% CIs (Month 1 analysis, ATP immunogenicity cohort) Endpoint dTpa-IPV/HPV HPV + dTpa-IPV dTpa-IPV/HPV minus HPV + dTpa-IPV

Endpoint	dTpa-IPV/HPV		HPV + dTpa-IPV		dTpa-IPV/HPV minus HPV + dTpa-IPV		
	N	%	N	%	Difference	95% CI	
						LL	UL
Diphtheria % ≥0.1 IU/ml	233	100	240	99.2	0.83	-0.80	2.99
Tetanus ≥0.1 IU/ml	233	100	240	100	0.00	-1.63	1.58
Polio type 1 ≥1:8 dilution	231	100	240	99.6	0.42	-1.23	2.33
Polio type 2 ≥1:8 dilution	232	100	240	100	0.00	-1.63	1.58
Polio type 3 ≥1:8 dilution	232	100	239	100	0.00	-1.63	1.59
					dTpa-IPV/HPV / HPV + dTpa-IPV		
	N	GMT	N	GMT	Ratio	95% CI	
						LL	UL
PT	229	75.4	238	84.2	0.90	0.74	1.09
FHA	233	615.2	240	611.7	1.01	0.87	1.16
PRN	233	360.0	239	426.2	0.84	0.67	1.07

HPV = HPV-16/18 L1 AS04 vaccine at Month 0,1,6; HPV+dTpa-IPV= dTpa-IPV at Month 0 and HPV-16/18 L1 AS04 vaccine at Month 0,1,6; dTpa-IPV/HPV = dTpa-IPV at Month 0 and HPV-16/18 L1 AS04 vaccine at Month 1,2,7; N = number of subjects with available results; % = percentage of subjects with titre within the specified range; 95% CI=95% standardised asymptotic CI; UL/LL=upper/lower limits.

Table 23: Differences in seroconversion rates and geometric mean titre (GMT) ratios one month after the third dose of HPV-16/18 L1 AS04 vaccine, with 95% CIs (Month 7 analysis, ATP immunogenicity cohort)

Endpoint	HPV		HPV + dTpa-IPV		HPV minus HPV + dTpa-IPV		
	N	%	N	%	Difference	95% CI	
						LL	UL
HPV-16 Seroconversion	198	100	202	99.5	0.50	-1.42	2.76
HPV-18 Seroconversion	191	100	204	99.5	0.49	-1.49	2.73
					HPV / HPV + dTpa-IPV		
	N	GMT	N	GMT	Ratio	95% CI	
						LL	UL
HPV-16	198	18965.1	202	15608.0	1.22	1.00	1.47
HPV-18	191	6902.4	204	6596.8	1.05	0.86	1.27

N = number of subjects with available pre-vaccination results; % = percentage seroconversion – initially seronegative subjects who became seropositive; 95% CI=95% standardised asymptotic confidence interval; UL/LL=upper/lower limits. See tables 30 and 31 in the study report.

In summary, results for each individual study group showed no differences between the HPV + dTpa-IPV co-administration group and HPV or dTpa-IPV/HPV control groups in terms of post-vaccination seroprotection/seroconversion/seropositivity/booster response rates, or in post-vaccination GMTs for each of the administered vaccine antigens. Overall, at least 96.9% of dTpa-IPV recipients had seroprotective antibody titres against diphtheria, tetanus, and poliovirus Types 1, 2 and 3, and were seropositive for antibodies against each pertussis antigen one month after the dTpa-IPV dose. At least 99.1% of all subjects (regardless of pre-vaccination status) were seropositive for antibodies against HPV-016 and HPV-018 one month after the first HPV-16/18 L1 AS04 vaccine dose and one month after the third HPV-16/18 L1 AS04 dose. Sequential administration of the dTpa-IPV and HPV-16/18 L1 AS04 vaccines tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to HPV-16/18 L1 AS04 administered alone but this is not likely to be of clinical significance as in all study groups, the GMTs were at least as high as the those previously reported in Studies HPV-008 and HPV-001/007.

Evaluator's Overall Conclusions on Clinical Efficacy

This is a very efficacious vaccine in preventing infection with HPV-16/18 and subsequent pre-malignant cervical changes, including the development of CIN2+ and CIN 3+. The large number of subjects and longer follow-up time in the final analysis of Study HPV-008 and the finding of statistically significant vaccine efficacy across multiple virological and histopathological endpoints and the consistency of these results with findings from the interim analysis of this study (Paavonen, 2007[6]) and findings from Studies HPV-001 and HPV-007 (Harper, 2008[7]) provide strong evidence of a protective effect of the HPV-16/18 L1 AS04 vaccine. As far as can be determined, these are well-designed, well controlled and well conducted studies. Importantly, there was a good correlation of vaccine efficacy results between 6-month persistent infection and other endpoints (12-month persistent infection, ASC-US+, CIN1+ or CIN2+) for HPV-16/18, as well as for these other oncogenic HPV types. The benefits of this

[6] Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet*. 2007; 369: 2161-2170.

[7] Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004; 364: 1757-65.

vaccine in preventing HPV 16/18 infection and histological changes as a result of this, in comparison to controls, were conclusively shown on all endpoints (except those with a very low incidence in the control group). This was so even in those subjects who had received an incomplete vaccination schedule, or a variation on the timing of vaccination.

The data from Study HPV-042 showed that the co-administration of the dTpa-IPV and HPV-16/18 L1 AS04 vaccines did not negatively impact on the immune response to either vaccine. Non-inferiority between combined and separately administered antigens was demonstrated for all antigens according to appropriate pre-specified criteria.

Safety

The assessment of the safety following vaccination with Cervarix was a secondary objective of Study HPV-007 and HPV-008. Safety data from HPV-042 is also included.

Adverse Events

HPV-007

In HPV-007, the incidence of adverse events (AEs), new onset chronic diseases (NOCDs) and new onset autoimmune diseases (NOADs) reported from the end of Study HPV-001 and throughout the entire HPV-007 follow-up period was similar or lower in the vaccine group than in the control group. A total of 82 non-fatal SAEs were reported for 70 subjects, of whom 31 in the vaccine group (36 cases) and 39 in the control group (46 cases). None of the SAEs were considered to be related to vaccination by the investigator. No fatal events were reported. The number of subjects with reports of an NOCD was low in the vaccine and placebo groups (5 [1.3%] and 6 [1.6%] subjects, respectively). Only one NOCD (pneumonitis) was considered as serious. The incidence of SAEs was slightly lower in the vaccine group (7.9%) compared to the placebo group (10.2%; results based on the Total cohort). None of the SAEs were considered as related to vaccination by the investigator. No fatal events were reported. The number of pregnancies resulting in abnormal outcomes was also lower in the vaccine group than in the control group, 19 (28.4%) compared with 29 (33.3%) cases, respectively. No safety issues were identified during the course of Study HPV-007. The safety analysis of this study did not show any clinically relevant differences between the vaccine and control groups and therefore indicates that Cervarix has an acceptable long-term safety profile.

HPV-008

In Study HPV-008 a subset of subjects from selected study sites (safety diary card subset: N ≥4,000, at least 1,000 per region) completed safety diary cards to record solicited local and general symptoms (Days 0-6) and unsolicited symptoms (Days 0-29) after each vaccination. As the final analysis of Study HPV-008 was event-driven, safety endpoints (SAEs, pregnancy outcomes and AEs related to NOCDs and medically significant conditions) were assessed up to the data lock-point (DLP) of 31 August 2008.

The primary analysis of solicited symptoms was based on the Interim Total Vaccinated cohort for solicited symptoms (safety diary card subset). The Total Vaccinated cohort comprises 18,644 subjects: 9,319 in the HPV group and 9,325 in the HAV group. Of the 18,644 subjects vaccinated, 1,725 subjects withdrew from the study before the final analysis. Most of these subjects (929 subjects) were lost to follow-up, 589 subjects withdrew their consent and 172 subjects migrated or moved from the study area. Fifteen subjects withdrew due to an SAE but none of these events reported as possibly related to vaccination according to the investigator. Eight subjects withdrew due to a non-serious AE, of which two events (one in each group) were considered as possibly related to vaccination according to the investigator. A further 12 subjects were withdrawn due to a protocol violation. Other reasons for withdrawal included mainly requests for unblinding (in order to receive a licensed HPV vaccine), termination (reasons

unknown), personal reasons and pregnancy. Compliance with the full vaccination course was equally high in both HPV and HAV groups: 91.6% in the HPV group and 91.9% in the HAV group. For analysis of safety based on the Total Vaccinated cohort, the mean follow-up period from Dose 1 was 40.8 months.

Summary of reactogenicity data (from interim analysis)

Solicited local symptoms (Safety Diary Card subset; interim cohort)

During the 7-day post-vaccination period, the percentage of doses followed by solicited local symptoms was higher in the HPV group (81.3%) compared to the HAV group (61.3%). The majority of symptoms were transient, with mean durations ranging from 2.2 to 3.4 days in both groups. Grade 3 solicited local symptoms were also more frequently reported in the HPV group (8.3%) than in the HAV group (2.0%). The higher relative incidence in the HPV group did not affect compliance with completion of the three-dose vaccination schedule (91.6% in the HPV group and 91.9% in the HAV group).

Solicited general symptoms (Safety Diary Card subset; interim cohort)

The incidence of solicited general symptoms within 7 days after vaccination was slightly higher in the HPV group compared to the HAV group (60.6% versus 53.9%, overall per dose). The incidence of solicited general symptoms assessed as Grade 3 (4.9% versus 3.4%, overall per dose), as possibly related to vaccination (40.8% versus 34.7%, overall per dose) or as Grade 3 and possibly related to vaccination (3.1% versus 2.0%, overall per dose) was also higher in the HPV group compared to the HAV group, respectively. The most common solicited general symptoms were fatigue, headache and myalgia. These were more frequently reported in the HPV group compared to the HAV group. The difference was most pronounced for myalgia (solicited reporting but not in the unsolicited reporting). When reported as an unsolicited symptom, myalgia was only observed in 0.5% to 0.6% of the subjects after 0.2% of doses in the HPV and HAV groups.

Unsolicited events (Safety Diary Card subset; interim cohort)

The incidence of unsolicited symptoms within 30 days after each dose was similar between the HPV and HAV groups (Table 24). In addition, a similar number of subjects in both groups reported a similar number of unsolicited symptoms assessed as Grade 3 (2.9% and 2.6%, overall per dose), as possibly related to vaccination according to the investigator (3.9% and 3.4%, overall per dose), or as Grade 3 and possibly related to vaccination according to the investigator (0.3% and 0.2%, overall per dose).

The most common unsolicited symptoms (≥1% of doses in both groups) were headache, influenza, gynaecological chlamydia infection, nasopharyngitis, pharyngolaryngeal pain and dizziness. All these events were reported after a similar percentage of doses in both groups. Compliance with the full vaccination course was equally high in both HPV and HAV groups (Table 25).

Table 24: Summary of Safety Endpoints

Percentage of subjects with at least one event (Total Vaccinated cohort)						
	HPV			HAV		
		95% CI			95% CI	
	%	LL	UL	%	LL	UL
Unsolicited symptoms (day 0-29)*	42.5	40.8	44.3	43.6	41.9	45.3
Serious adverse events	7.5	7.0	8.1	7.5	7.0	8.0
Medically significant conditions	31.8	30.8	32.7	32.4	31.5	33.4
New Onset Chronic Diseases**	2.7	2.4	3.0	2.9	2.5	3.2
New Onset Autoimmune Diseases	0.8	0.7	1.0	0.8	0.7	1.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots) %= percentage of subjects reporting at least once the symptom 95% CI = exact 95% confidence interval, LL = Lower

Limit, UL = Upper Limit * Unsolicited symptoms were reported during the 30-day post-vaccination period by subjects included in the safety diary card subset (based on Interim Total Vaccinated cohort). All other events were reported during the entire follow up period (based on Final Total Vaccinated cohort). ** GSK assessment

HPV-042

The adverse events following vaccination with acellular pertussis-containing vaccines are well characterised. The incidence of systemic adverse events following acellular pertussis vaccines is low, when compared to the incidence following vaccination with whole cell pertussis vaccines. Studies that evaluated a booster dose of reduced antigen content dTpa and dTpa-IPV vaccines (*Boostrix* and *Boostrix Polio)* in adolescents showed that pain following vaccination was common, reported in up to 90% of subjects. The HPV-16/18 L1 AS04 vaccine has been associated with local pain, redness and swelling soon after vaccination. Fatigue and myalgia have also been reported up to 7 days post-vaccination. Reactogenicity and safety was evaluated in all subjects enrolled in Study HPV-042. Local symptoms (pain, redness and swelling) and general symptoms (fever, headache, fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash and urticaria) were solicited for 7 days following each vaccination using diary cards. In addition to solicited symptoms, all other adverse events that occurred in the 30 day period following vaccination were recorded as unsolicited symptoms.

Table 25: Summary of solicited and unsolicited symptoms

		HPV			HAV		
Solicited symptoms: percentage of doses with events within 7 days after vaccination in the safety diary card subset (Interim Total Vaccinated cohort)							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Pain	All	80.2	79.3	81.0	58.9	57.8	59.9
	Grade 3	7.3	6.8	7.9	1.8	1.5	2.1
Redness	All	28.1	27.2	29.1	16.0	15.2	16.8
	> 50.0 mm	0.4	0.3	0.6	0.0	0.0	0.1
Swelling	All	25.4	24.5	26.3	10.1	9.5	10.8
	> 50.0 mm	1.0	0.8	1.2	0.2	0.1	0.3
Arthralgia	All	10.7	10.0	11.3	8.6	8.0	9.2
	Grade 3	0.4	0.3	0.5	0.3	0.2	0.4
Fatigue	All	38.8	37.8	39.9	35.3	34.3	36.3
	Grade 3	1.6	1.4	1.9	1.3	1.1	1.6
Fever	All	5.3	4.8	5.8	4.6	4.1	5.0
	> 39.0°C	0.2	0.1	0.3	0.1	0.1	0.2
Gastrointestinal	All	14.3	13.6	15.1	14.0	13.3	14.7
	Grade 3	0.7	0.6	0.9	0.7	0.5	0.9
Headache	All	32.9	31.9	33.9	30.8	29.8	31.8
	Grade 3	1.7	1.4	2.0	1.4	1.1	1.6
Myalgia	All	34.3	33.3	35.3	26.5	25.6	27.5
	Grade 3	1.8	1.5	2.1	0.6	0.4	0.8
Rash	All	4.4	4.0	4.9	3.6	3.2	4.0
	Grade 3	0.1	0.0	0.2	0.1	0.0	0.1
Urticaria	All	4.6	4.2	5.1	3.7	3.3	4.1
	Grade 3	0.3	0.2	0.5	0.4	0.2	0.5
Percentage of subjects with at least one event (Total Vaccinated cohort)*							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Unsolicited symptom (day 0-29)		42.5	40.8	44.3	43.6	41.9	45.3
SAE		7.5	7.0	8.1	7.5	7.0	8.0
Medically significant condition		31.8	30.8	32.7	32.4	31.5	33.4
NOCD		2.7	2.4	3.0	2.9	2.5	3.2
NOAD		0.8	0.7	1.0	0.8	0.7	1.0

HPV and HAV as above. %= percentage of subjects reporting at least once the symptom. 95% CI, LL and UL as above. * Events were reported during the entire follow-up period (based on Final Total Vaccinated

cohort), except for unsolicited symptoms (30-day post-vaccination period, based on Interim Total Vaccinated cohort). Note: Data from interim analysis for solicited and unsolicited (Day 0-29) symptoms

Common and non-serious adverse events

The incidences of solicited local and general adverse events after Dose 1, at which time subjects in the co-administration group received simultaneous vaccination with dTpa-IPV and HPV-16/18 L1 AS04, and subjects in the control groups received HPV-16/18 L1 AS04 alone (Group HPV) or dTpa-IPV alone (Group, dTpa-IPVHPV) are summarised in Table 26. After Dose 1, the point estimate for the incidence of all local and general symptoms, except gastrointestinal symptoms and urticaria, was higher in the co-administration group (HPV + dTpa-IPV) compared to the two control groups. However the 95% CIs overlapped between the co-administration and separate vaccine groups for all comparisons.

Table 26: Incidence of solicited local and general symptoms reported during the 7-day (Days 0-6) period following Dose 1 (Month 7/8 analysis, Total vaccinated cohort)

Symptom	Type	HPV					HPV+dTpa-IPV					dTpa-IPV/HPV				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL				LL	UL
Pain	All	246	209	85.0	79.9	89.2	253	226	89.3	84.9	92.8	247	207	83.8	78.6	88.2
	Grade 3	246	15	6.1	3.5	9.9	253	22	8.7	5.5	12.9	247	11	4.5	2.2	7.8
Redness	All	246	69	28.0	22.5	34.1	253	87	34.4	28.6	40.6	247	83	33.6	27.7	39.9
	>50 mm	246	2	0.8	0.1	2.9	253	8	3.2	1.4	6.1	247	5	2.0	0.7	4.7
Swelling	All	246	62	25.2	19.9	31.1	253	79	31.2	25.6	37.3	247	75	30.4	24.7	36.5
	>50 mm	246	4	1.6	0.4	4.1	253	5	2.0	0.6	4.6	247	6	2.4	0.9	5.2
Arthralgia	All	246	32	13.0	9.1	17.9	253	44	17.4	12.9	22.6	247	33	13.4	9.4	18.2
	Grade 3	246	0	0.0	0.0	1.5	253	3	1.2	0.2	3.4	247	2	0.8	0.1	2.9
Fatigue	All	246	73	29.7	24.0	35.8	253	104	41.1	35.0	47.4	247	88	35.6	29.7	41.9
	Grade 3	246	3	1.2	0.3	3.5	253	9	3.6	1.6	6.6	247	2	0.8	0.1	2.9
Fever/(Axillary)	≥37.5°C	246	14	5.7	3.1	9.4	253	24	9.5	6.2	13.8	247	18	7.3	4.4	11.3
	>39.0°C	246	1	0.4	0.0	2.2	253	1	0.4	0.0	2.2	247	2	0.8	0.1	2.9
Gastrointestinal	All	246	28	11.4	7.7	16.0	253	35	13.8	9.8	18.7	247	36	14.6	10.4	19.6
	Grade 3	246	0	0.0	0.0	1.5	253	6	2.4	0.9	5.1	247	0	0.0	0.0	1.5
Headache	All	246	73	29.7	24.0	35.8	253	95	37.5	31.6	43.8	247	83	33.6	27.7	39.9
	Grade 3	246	1	0.4	0.0	2.2	253	5	2.0	0.6	4.6	247	4	1.6	0.4	4.1
Myalgia	All	246	71	28.9	23.3	35.0	253	97	38.3	32.3	44.6	247	87	35.2	29.3	41.5
	Grade 3	246	3	1.2	0.3	3.5	253	8	3.2	1.4	6.1	247	7	2.8	1.1	5.8
Rash	All	246	6	2.4	0.9	5.2	253	11	4.3	2.2	7.6	247	10	4.0	2.0	7.3
	Grade 3	246	0	0.0	0.0	1.5	253	1	0.4	0.0	2.2	247	0	0.0	0.0	1.5
Urticaria	All	246	7	2.8	1.2	5.8	253	6	2.4	0.9	5.1	247	7	2.8	1.1	5.8
	Grade 3	246	0	0.0	0.0	1.5	253	0	0.0	0.0	1.4	247	0	0.0	0.0	1.5

HPV = HPV-16/18 L1 AS04 vaccine at Month 0,1,6; HPV+dTpa-IPV= dTpa-IPV at Month 0 and HPV-16/18 L1 AS04 vaccine at Month 0,1,6; dTpa-IPV/HPV = dTpa-IPV at Month 0 and HPV-16/18 L1 AS04 vaccine at Month 1,2,7; N= number of subjects with at least one documented dose, n/%= umber/percentage of subjects reporting the symptom at least once. For Overall/dose: N= number of documented doses; n/%= number/percentage of doses with at least one local symptom whatever the number of injections.

Although the estimated incidence of Grade 3 symptoms was observed to be higher for many local and general symptoms after Dose 1, the 95% CIs overlapped in all cases. In all groups pain was the most commonly reported Grade 3 symptom and occurred in between 4.5% to 8.7% of subjects in each group. Grade 3 systemic symptoms were reported in no more than 3.6% of subjects in any group. The incidences of solicited local and general adverse events after all vaccine doses are given in Table 27. Pain was the most frequently reported solicited local symptom in all groups and was reported after 74.4% to 77.1% of all doses. Most solicited local symptoms were mild to moderate in intensity and resolved within 4 days. The most frequently reported general symptoms in all groups were fatigue, headache and myalgia. Myalgia was reported more frequently (no overlap of 95% CIs) in the HPV + dTpa-IPV co-administration group (after 33.4% [95% CI 30.1; 36.9] of all doses) than the HPV group (after 26.4% [95% CI 23.3; 29.8] of doses) and tended to be more frequently reported in the HPV + dTpa-IPV group

compared to the dTpa-IPV/HPV group (27.4% [95% CI 24.6; 30.3]). Headache was reported more frequently in the HPV + dTpa-IPV group compared to the dTpa- IPV/HPV group (29.3 % [95% CI 26.1; 32.7] versus 22.5% [95% CI 19.9; 25.2]). Grade 3 headache and myalgia occurred after no more than 1.8% of doses and was within the same range in each group. Pain was the most commonly reported Grade 3 solicited symptom overall doses (between 4.5% and 5.2% of doses). Most of these symptoms resolved within 3 days. Other solicited Grade 3 symptoms were reported after no more that 2.1% of all doses and were generally within the same range across groups. The majority of Grade 3 solicited general symptoms were considered by the investigator to be related to vaccination. Most solicited general symptoms resolved within 3-5 days. No increase in symptoms was observed at subsequent doses. No subjects reported urticaria/rash within 30 minutes of vaccination in any group.

Table 27: Incidence of solicited local and general symptoms reported during the 7-day (Days 0-6) period overall doses (Month 7/8 analysis, Total vaccinated cohort)

Symptom	Type	HPV					HPV+dTpa-IPV					dTpa-IPV/HPV				
		N	n	%	95 % CI		N	n	%	95 % CI		N	n	%	95 % CI	
					LL	UL				LL	UL				LL	UL
Pain	All	734	566	77.1	73.9	80.1	754	570	75.6	72.4	78.6	983	731	74.4	71.5	77.1
	Grade 3	734	36	4.9	3.5	6.7	754	39	5.2	3.7	7.0	983	44	4.5	3.3	6.0
Redness	All	734	197	26.8	23.7	30.2	754	221	29.3	26.1	32.7	983	292	29.7	26.9	32.7
	>50 mm	734	6	0.8	0.3	1.8	754	11	1.5	0.7	2.6	983	6	0.6	0.2	1.3
Swelling	All	734	209	28.5	25.2	31.9	754	203	26.9	23.8	30.2	983	262	26.7	23.9	29.5
	>50 mm	734	11	1.5	0.8	2.7	754	9	1.2	0.5	2.3	983	9	0.9	0.4	1.7
Arthralgia	All	734	83	11.3	9.1	13.8	754	101	13.4	11.0	16.0	983	125	12.7	10.7	15.0
	Grade 3	734	5	0.7	0.2	1.6	754	6	0.8	0.3	1.7	983	6	0.6	0.2	1.3
Fatigue	All	734	175	23.8	20.8	27.1	754	216	28.6	25.4	32.0	983	237	24.1	21.5	26.9
	Grade 3	734	13	1.8	0.9	3.0	754	16	2.1	1.2	3.4	983	8	0.8	0.4	1.6
Fever/(Axillary)	≥37.5°C	734	36	4.9	3.5	6.7	754	53	7.0	5.3	9.1	983	50	5.1	3.8	6.7
	>39.0°C	734	5	0.7	0.2	1.6	754	1	0.1	0.0	0.7	983	6	0.6	0.2	1.3
Gastrointestinal	All	734	71	9.7	7.6	12.0	754	83	11.0	8.9	13.5	983	83	8.4	6.8	10.4
	Grade 3	734	2	0.3	0.0	1.0	754	14	1.9	1.0	3.1	983	5	0.5	0.2	1.2
Headache	All	734	177	24.1	21.1	27.4	754	221	29.3	26.1	32.7	983	221	22.5	19.9	25.2
	Grade 3	734	9	1.2	0.6	2.3	754	11	1.5	0.7	2.6	983	9	0.9	0.4	1.7
Myalgia	All	734	194	26.4	23.3	29.8	754	252	33.4	30.1	36.9	983	269	27.4	24.6	30.3
	Grade 3	734	7	1.0	0.4	2.0	754	13	1.7	0.9	2.9	983	18	1.8	1.1	2.9
Rash	All	734	20	2.7	1.7	4.2	754	30	4.0	2.7	5.6	983	21	2.1	1.3	3.2
	Grade 3	734	0	0.0	0.0	0.5	754	1	0.1	0.0	0.7	983	0	0.0	0.0	0.4
Urticaria	All	734	12	1.6	0.8	2.8	754	12	1.6	0.8	2.8	983	19	1.9	1.2	3.0
	Grade 3	734	0	0.0	0.0	0.5	754	0	0.0	0.0	0.5	983	0	0.0	0.0	0.4

HPV = HPV-16/18 L1 AS04 vaccine at Month 0,1,6; HPV+dTpa-IPV= dTpa-IPV at Month 0 and HPV-16/18 L1 AS04 vaccine at Month 0,1,6; dTpa-IPV/HPV = dTpa-IPVat Month 0 and HPV-16/18 L1 AS04 vaccine at Month 1,2,7; N= number of subjects with at least one documented dose, n/%= number/percentage of subjects reporting the symptom at least once. For Overall/dose: N= number of documented doses; n/%= number/percentage of doses with at least one local symptom whatever the number of injections. 95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit.

Unsolicited symptoms

The percentage of doses followed by at least one unsolicited symptom within the 30-day post vaccination period was within the same range in each group: 15.4% in the HPV group, 12.5% in the HPV+dTpa-IPV group and 14.0% in the dTpa-IPV/HPV group. Grade 3 unsolicited symptoms were reported after 0.4% or 0.5% of doses in each group.

Concomitant medication

The use of concomitant medication overall per dose during the 7-day post-dose vaccination period was 13.8% for the HPV group, 14.5% for the HPV+dTpa-IPV group and 11.8% for the dTpa-IPV/HPV group. Over all doses, antipyretics were used by 9.9% of the subjects in the HPV group, 11.1% of the subjects in the HPV+dTpa-IPV group and 7.5% of the subjects in the dTpa-

IPV/HPV group during the 7-day post vaccination period. The proportion of subjects using concomitant medication/vaccination was similar between groups for both the 7-day and the 30-day period following any of the doses. No differences were observed between groups for antipyretics or antibiotics.

Serious Adverse Events and Deaths

HPV-008

Of the 18644 subjects included in the Total Vaccinated cohort, 1400 subjects (701 in the HPV group and 699 in the HAV group) reported a total of 1724 SAEs. The most frequently reported SAEs were related to infections and abnormal pregnancy outcomes. The observed incidences in this analysis reflect those in the general population. The number of subjects reporting SAEs which were considered by the investigator as possibly related to vaccination was low in both groups (eleven in the HPV group and six in the HAV group [0.1% in each group]). Analysis of the individual events revealed no clinical patterns or clinically relevant imbalances between the HPV and HAV groups.

No further doses of vaccine have been administered in Study HPV-008 since the interim analysis. The adverse events related to vaccination previously are described below. During the 7-day post-vaccination period, the percentage of doses followed by solicited local symptoms was higher in the HPV group (81.3%) compared to the HAV group (61.3%). The majority of symptoms were transient, with mean durations ranging from 2.2 to 3.4 days in both groups. Grade 3 solicited local symptoms were also more frequently reported in the HPV group (8.3%) than in the HAV group (2.0%). The higher relative incidence in the HPV group did not affect compliance with completion of the three-dose vaccination schedule (91.6% in the HPV group and 91.9% in the HAV group). The incidence of unsolicited symptoms within 30 days after each dose was similar between the HPV and HAV groups (Table 28). In addition, a similar number of subjects in both groups reported a similar number of unsolicited symptoms assessed as Grade 3 (2.9% and 2.6%, overall per dose), as possibly related to vaccination according to the investigator (3.9% and 3.4%, overall per dose), or as Grade 3 and possibly related to vaccination according to the investigator (0.3% and 0.2%, overall per dose).

Table 28: Summary of Safety Endpoints (table continued across two pages)

Percentage of subjects with at least one event (Total Vaccinated cohort)						
	HPV			HAV		
		95% CI			95% CI	
	%	LL	UL	%	LL	UL
Unsolicited symptoms (day 0-29)*	42.5	40.8	44.3	43.6	41.9	45.3
Serious adverse events	7.5	7.0	8.1	7.5	7.0	8.0
Medically significant conditions	31.8	30.8	32.7	32.4	31.5	33.4
New Onset Chronic Diseases**	2.7	2.4	3.0	2.9	2.5	3.2
New Onset Autoimmune Diseases	0.8	0.7	1.0	0.8	0.7	1.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots). %= percentage of subjects reporting at least once the symptom. * Unsolicited symptoms were reported during the 30-day post-vaccination period by subjects included in the safety diary card subset (based on Interim Total Vaccinated cohort). All other events were reported during the entire followup period (based on Final Total Vaccinated cohort). ** GSK assessment

The most common unsolicited symptoms (≥1% of doses in both groups) were headache, influenza, gynecological chlamydia infection, nasopharyngitis, pharyngolaryngeal pain and dizziness (Table 29). All these events were reported after a similar percentage of doses in both groups.

Table 29: Summary of solicited and unsolicited symptoms

		HPV			HAV		
Solicited symptoms: percentage of doses with events within 7 days after vaccination in the safety diary card subset (Interim Total Vaccinated cohort)							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Pain	All	80.2	79.3	81.0	58.9	57.8	59.9
	Grade 3	7.3	6.8	7.9	1.8	1.5	2.1
Redness	All	28.1	27.2	29.1	16.0	15.2	16.8
	> 50.0 mm	0.4	0.3	0.6	0.0	0.0	0.1
Swelling	All	25.4	24.5	26.3	10.1	9.5	10.8
	> 50.0 mm	1.0	0.8	1.2	0.2	0.1	0.3
Arthralgia	All	10.7	10.0	11.3	8.6	8.0	9.2
	Grade 3	0.4	0.3	0.5	0.3	0.2	0.4
Fatigue	All	38.8	37.8	39.9	35.3	34.3	36.3
	Grade 3	1.6	1.4	1.9	1.3	1.1	1.6
Fever	All	5.3	4.8	5.8	4.6	4.1	5.0
	> 39.0°C	0.2	0.1	0.3	0.1	0.1	0.2
Gastrointestinal	All	14.3	13.6	15.1	14.0	13.3	14.7
	Grade 3	0.7	0.6	0.9	0.7	0.5	0.9
Headache	All	32.9	31.9	33.9	30.8	29.8	31.8
	Grade 3	1.7	1.4	2.0	1.4	1.1	1.6
Myalgia	All	34.3	33.3	35.3	26.5	25.6	27.5
	Grade 3	1.8	1.5	2.1	0.6	0.4	0.8
Rash	All	4.4	4.0	4.9	3.6	3.2	4.0
	Grade 3	0.1	0.0	0.2	0.1	0.0	0.1
Urticaria	All	4.6	4.2	5.1	3.7	3.3	4.1
	Grade 3	0.3	0.2	0.5	0.4	0.2	0.5
Percentage of subjects with at least one event (Total Vaccinated cohort)*							
			95% CI			95% CI	
		%	LL	UL	%	LL	UL
Unsolicited symptom (day 0-29)		42.5	40.8	44.3	43.6	41.9	45.3
SAE		7.5	7.0	8.1	7.5	7.0	8.0
Medically significant condition		31.8	30.8	32.7	32.4	31.5	33.4
NOCD		2.7	2.4	3.0	2.9	2.5	3.2
NOAD		0.8	0.7	1.0	0.8	0.7	1.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots). HAV = Hepatitis A vaccine (three lots). %= percentage of subjects reporting at least once the symptom. 95% CI, LL and UL as above.* Events were reported during the entire follow-up period (based on Final Total Vaccinated cohort), except for unsolicited symptoms (30-day post-vaccination period, based on Interim Total Vaccinated cohort)

New Onset Chronic Diseases (NOCD) and New Onset Autoimmune Diseases (NOAD)

The percentage of subjects experiencing an NOCD as assessed by investigators was low and comparable between the HPV and HAV groups (see Tables 28 and 29). The most common NOCDs were asthma, urticaria, hypersensitivity, hypothyroidism and seasonal allergy. All were reported with a similar low incidence in both groups (≤0.4% of subjects). No imbalances between the groups were observed for any event.

Pregnancy outcomes

At the time of the final analysis of Study HPV-008, 3,606 pregnancies were reported (1804 in the HPV group and 1802 in the HAV group) in 3,091 subjects (1,538 in the HPV group and 1,553 in the HAV group) over the entire follow-up period. Around the time of vaccination (that is, in pregnant women who had their last menstrual period [LMP] between 30 days before and 45 days after vaccination), 369 pregnancies were reported (190 in the HPV group and 179 in the HAV group). Twenty-two fetal, neonatal or infant deaths were reported (11 cases in each group). When analysed over the entire study period, no major differences in the rates of any

specific pregnancy outcome were observed between the HPV and HAV groups. The proportion of pregnancies ending in spontaneous abortion was similar between the two study groups (9.1% versus 8.7%). The proportion of spontaneous abortions reported in pregnant women who had their LMP between 30 days before and 45 days after vaccination was 11.6% the HPV group and 5.0% in the HAV group. This imbalance was mostly observed in women who had their LMP within 30 days prior to immunization. No conclusions can be drawn, due to the low number of cases. There was no evidence of higher occurrence of spontaneous abortion after a specific dose or at a specific age. The mean gestational age at which the spontaneous abortions occurred did not differ substantially between treatment groups or from background rates. The observed rates of spontaneous abortions following HPV vaccine administration (9.1% for pregnancies overall and 11.6% for pregnancies around vaccination) are in the range of published incidence rates of spontaneous abortion. The number of abnormal infants for pregnancies overall was equally distributed across treatment groups (21 [1.2%] in the HPV group versus 19 [1.1%] in the HAV group).

Medically Significant Conditions (MSC)

Medically significant conditions (MSC) were reported in a similar percentage of subjects in the HPV and HAV groups (see Table 29). The most common medically significant conditions were gynecological chlamydia infection, genito-urinary tract gonococcal infection and depression, all of which were reported in similar percentages of subjects in the HPV and HAV groups (9.8% versus 10.2%, 1.5% versus 1.7% and 1.5% each, respectively). Subjects were screened for *Chlamydia trachomatis* and *Neisseria gonorrhea* infection on a yearly basis and this explains the frequent reporting of these conditions.

Study HPV-042

Eight subjects reported eight serious adverse events during the study until the end of the 30-day period after the last study vaccine dose. None of the serious adverse events were considered to be related to vaccination by the investigator. Two pregnancies were reported during the study. One subject (HPV + dTpa-IPV group) experienced imminent abortion three months after the first combined vaccine dose but the pregnancy continued and the subject gave birth to a healthy female infant at term. No outcome for the second subjects was known at the time of the database freeze. There were no deaths during the study period of 8 months .

New onset of chronic disease (NOCD)

During the entire follow up period there were 28 different NOCD reported in 23 subjects. None of these events were classified as serious adverse events:

- HPV group: five subjects (2.0%) reported six new onset of chronic disease. These subjects were diagnosed with hypersensitivity (two cases), seasonal allergy (two cases), paraesthesia and dermatitis allergic;
- HPV + dTpa-IPV group: nine subjects (3.5%) diagnosed with hypothyroidism, hypersensitivity (two cases), arthritis, asthma, rhinitis allergic (three cases), psoriasis and urticaria.
- dTpa-IPV/HPV group: nine subjects (3.6%) diagnosed with conjunctivitis allergic, allergy to animal, hypersensitivity (three cases), seasonal allergy (two cases), asthma, rhinitis allergic and dermatitis allergic (two cases).

Discontinuation Due To Adverse Events

Adverse events (AEs) leading to premature discontinuation in Study-HPV-008 were uncommon during this study; eight subjects withdrew from the study due to a non-serious AE (five in the HPV group and three in the HAV group) and 15 subjects withdrew due to SAEs (seven in the HPV group and eight in the HAV group). No subjects were withdrawn from Study HPV-042 due to an AE during the entire study period.

Post Marketing Experience-Worldwide marketing

Cervarix was first approved in Australia on the 18 May 2007. In a number of countries it is widely distributed to adolescent girls as part of school-based immunisation programs. Table 30 presents the reporting frequency of events for *Cervarix* arising from spontaneous reporting. This analysis included all serious and non-serious events from launch (18th May, 2007) up to the date of the most recent data of the current Periodic Safety Update Report (PSUR) (17th November, 2008). Listed events are indicated in bold. The events were reported with a frequency between 1.14 and 3.33 per 100,000 doses distributed. The most frequently reported events are: injection site pain (3.33 cases per 100,000 doses distributed) followed by headache (3.12 cases per 100,000 doses distributed) and pyrexia (2.78 cases per 100,000 doses distributed).

Table 30: Frequency of 10 most reported events (all spontaneous cases) per 100,000 doses distributed

Event SOC	Event PT	Number Of Events	Reported Frequency per 100,000 doses distributed
General disorders and administration site conditions	**Injection site pain**	128	3.33
Nervous system disorders	**Headache**	120	3.12
General disorders and administration site conditions	**Pyrexia**	107	2.78
Social circumstances	Pharmaceutical product complaint	104	2.71
Nervous system disorders	**Dizziness**	91	2.37
Gastrointestinal disorders	**Nausea**	83	2.16
Musculoskeletal and connective tissue disorders	Pain in extremity	70	1.82
Skin and subcutaneous tissue disorders	**Rash**	66	1.72
General disorders and administration site conditions	Malaise	65	1.69
Musculoskeletal and connective tissue disorders	**Myalgia**	44	1.14

No fatalities have been reported to GSK since the introduction of *Cervarix* on the market.

Product Information (PI) With Respect To Safety

Since no safety issues were identified during the course of Study HPV-007, GSK have not requested any changes to the safety section of the Prescribing Information (PI). The adverse events reported in the final report of HPV-008 did not include any new or unexpected events. In Study HPV-007, myalgia was more common with the combined vaccination, but this adverse event is already documented.

Evaluator's Overall Conclusions on Clinical Safety

In relation to safety, no new adverse events have been identified in the final reports of HPV-007 or HPV-008. Nor have there been any definite relationship to either new onset chronic diseases or adverse pregnancy outcomes. As expected, there is a fairly high incidence of solicited adverse events related to vaccination which are generally non-serious. The most common localised AEs are redness, pain and swelling at the injection site. The most common generalised AEs are myalgia, arthralgia, fatigue and fever. In Study HPV-042, of note is that myalgia is more common when the two vaccines are co-administered, but this symptom generally is not serious.

Clinical Evaluation Report 2

The following is an addendum (Clinical Evaluation Report 2; CER2) to the original clinical evaluation report, following evaluation of supplementary data submitted by the sponsor.

What does the supplementary data comprise of?

The dossier for this submission consisted of clinical data only. Towards the final stages of completion of evaluation the sponsor informed the TGA that the ongoing End of Study analysis of the Study HPV-008 had led to discovery of some inaccuracies in the event-triggered Final analysis, requiring some modification of the study report provided earlier.

A full amended study report was obtained from the sponsor and evaluated as supplementary data. This addendum is limited to documenting the differences that arose out of reanalysis and interpretation, if any.

This was a randomised, double-blind, (placebo)-controlled trial designed to evaluate the efficacy of HPV-16/18 Virus Like Particle AS04-adjuvanted vaccine (Cervarix) for protection against HPV-16/18 associated CIN2+ lesions, and was carried out in young women (15-25 years old) irrespective of HPV exposure status at the baseline.

The study was large (N > 18,000) and multinational including Australia. The control group received hepatitis A vaccine using same administration schedule.

Three efficacy analyses had been specified in the protocol for this study as follows:

1. An event-triggered interim analysis when at least 23 HPV-16/18 associated CIN2+ cases had been accrued in the TVC-1.

The results have been previously evaluated and are currently included in the approved Cervarix PI. These are not affected by the reanalysis.

2. An event-triggered Final analysis when at least 36 HPV-16/18 associated CIN2+ cases had been accrued in the According-to-Protocol Cohort of Efficacy (ATP).

The results were part of the package for the current submission and are the subject of this addendum due to reanalysis.

3. The End of Study (completion of all follow-up) analysis is currently ongoing and is not included in the current submission.

The Final analysis has been re-done using only the protocol-defined PCR algorithm. This addendum highlights the differences compared to those reported in the original CER (CER1).

What led to the reanalysis?

During the course of End of Study analysis, an inconsistency was discovered between the End of Study data and the previous Final analysis data with respect to the virological endpoints (HPV-DNA in cervical samples).

Further investigation showed that poor specificity in the statistical program resulted in virological endpoints at the time of Final analysis to be assigned not only based on the protocol-specified PCR algorithm (LiPA followed by type-specific PCR for HPV-16 and HPV-18) as should have happened, but had also incorporated the results of an exploratory PCR called Multiplex Type Specific PCR (MPTS-PCR) which had been tested in a subset of participants.

The MPTS-PCR is being developed as a more sensitive type-specific PCR for detection of nine HPV types (16, 18, 31, 33, 35, 45, 52, 58 and 59). The testing was in accordance with the study protocol as part of validation of MPTS-PCR methodology.

The results from MPTS-PCR were to be entered into the database but were not to be included in the protocol-defined endpoint in HPV-008 efficacy analyses. Hence, at the time of previously reported Final analysis, a sample was considered PCR positive for a HPV type if at least one of the three PCR tests (LiPA, type-specific 16/18 PCR or MPTS-PCR) returned positive for that HPV type.

The error led to an overestimation of a number of virological endpoints associated with the nine HPV types targeted by the MPTS-PCR.

It should be noted that for HPV types 16 and 18, as the results from two PCR tests (LiPA and type-specific 16/18 PCR) had already been taken into account, the use of the new MPTS-PCR resulted in very small number of additional cases.

For some non-vaccine (non 16/18) HPV types, the number of additional cases detected was greater due to the higher sensitivity of MPTS-PCR compared to LiPA for these types.

Which outcomes were affected?

The MPTS-PCR testing was performed on cervical samples, and not on biopsies. As a result, the histopathological endpoints defined by HPV-DNA detection on biopsies were not impacted. The following outcomes are potentially impacted:

i. Virological endpoints for the 9 HPV types covered by the MPTS-PCR:

These are secondary endpoints (6-month and 12-month persistent infection with HPV-16/18 and 6-month persistent infection with oncogenic HPV types) and exploratory endpoints (for example, 12-month persistent infection with oncogenic HPV types and incident infection and abnormal cytology [ASCUS+] associated with HPV-16/18 or other oncogenic HPV types).

ii. Histopathological endpoints defined using the HPV Type Assignment Algorithm (TAA) in which the case is not only defined by the HPV type detected in the biopsy but also by taking into account the HPV type in one of the two preceding cervical samples. The HPV TAA (also called clinical case assignment) is an exploratory analysis aiming to increase the specificity of causal association of a CIN lesion with a specific HPV type when DNA for multiple HPV types was detected in the lesion.

iii. Immunogenicity endpoints were affected due to change in the number of subjects in the ATP cohort for immunogenicity. A total of 55 subjects could no longer be eliminated because of presence of concomitant infection related to the vaccine which may influence immune response. Of these 55 subjects, 10 were in the subset for immunogenicity (7 in the HPV group and 3 in the HAV group). Based on the protocol-specified PCR results, these 10 subjects needed to be included in the ATP cohort for immunogenicity.

Results following reanalyses of Study HPV-008

Primary variable

The overall treatment effect and the statistical significance remained unchanged for protocol-defined primary and secondary outcomes. The results for various analyses looking at the primary efficacy outcome were as follows and were unaffected by the reanalysis:

Table 31: **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(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16/18	HPV	7344	4	17689.60	0.02	0.01	0.06	92.9	79.9	98.3	<0.0001
	HAV	7312	56	17663.32	0.32	0.24	0.42	-	-	-	-
HPV-16	HPV	6303	2	15193.63	0.01	0.00	0.05	95.7	82.9	99.6	<0.0001
	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	0.0013
	HAV	6746	15	16310.82	0.09	0.05	0.16	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
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
P-value=Two-sided Fisher Exact test

The primary analysis using ATP cohort was consistent with the analysis using TVC-1 population which was a complementary analysis. The results were as follows:

Table 32: **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 (TVC-1)**

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16/18	HPV	8040	5	23215.10	0.02	0.01	0.05	94.5	86.2	98.4	<0.0001
	HAV	8080	91	23297.14	0.39	0.31	0.48	-	-	-	-
HPV-16	HPV	6921	3	20013.94	0.01	0.00	0.05	95.9	87.0	99.3	<0.0001
	HAV	6923	73	19998.76	0.37	0.28	0.46	-	-	-	-
HPV-18	HPV	7455	2	21544.80	0.01	0.00	0.04	91.6	64.6	99.2	<0.0001
	HAV	7480	24	21618.46	0.11	0.07	0.17	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (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 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
P-value=Two-sided Fisher Exact test

The exploratory HPV-TAA analysis also supported the primary results:

Table 33:

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16/18	HPV	7344	1	17695.52	0.01	0.00	0.03	98.1	88.4	100	<0.0001
	HAV	7312	53	17666.23	0.30	0.22	0.40	-	-	-	-
HPV-16	HPV	6303	0	15197.83	0.00	0.00	0.03	100	91.0	100	<0.0001
	HAV	6165	45	14911.61	0.30	0.22	0.41	-	-	-	-
HPV-18	HPV	6794	1	16379.68	0.01	0.00	0.04	92.3	45.7	99.9	0.0009
	HAV	6746	13	16313.61	0.08	0.04	0.14	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
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
P-value=Two-sided Fisher Exact test

The incidence of CIN+3 lesions in TVC-1 population was as follows:

Table 34:

Incidence rates and vaccine efficacy against CIN3+ associated with HPV-16 and/or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method (TVC-1)

					Person-year rate			VE			
Event Type	Group	N	n	T(year)	n/T (Per 100)	LL	UL	%	LL	UL	P-value
HPV-16/18	HPV	8040	2	23219.03	0.01	0.00	0.03	90.9	60.8	99.1	<0.0001
	HAV	8080	22	23358.12	0.09	0.06	0.15	-	-	-	-
HPV-16	HPV	6921	2	20015.57	0.01	0.00	0.04	87.5	43.8	98.8	0.0013
	HAV	6923	16	20042.43	0.08	0.04	0.13	-	-	-	-
HPV-18	HPV	7455	0	21547.09	0.00	0.00	0.02	100	24.2	100	0.0156
	HAV	7480	7	21638.49	0.03	0.01	0.07	-	-	-	-

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots)
HAV = Hepatitis A vaccine (three lots)
CIN3+ = CIN3, AIS or invasive cervical cancer
N=number of subjects included in each group
For single type: Subjects DNA negative and seronegative for the corresponding HPV type at Month 0
For combined types: Subjects DNA negative and seronegative for at least one HPV type at Month 0 (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 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
P-value=Two-sided Fisher Exact test

Secondary and other exploratory variables:

The results for a number of secondary and exploratory virological and histopathological endpoints were required amending due to reduction in the number of cases and consequent change in width of 96.1% confidence intervals and loss of statistical significance in some.

The changes in immunogenicity outcomes (seropositive rates and geometric mean titres) were small and did not affect the conclusions.

The tables on the following pages indicate differences from the previously reported summary data, where relevant:

Table 35: Summary of vaccine efficacy against virological and histopathological endpoints associated with HPV-16/18 in subjects HPV DNA negative and seronegative at baseline (ATP cohort for efficacy)

	HPV	HAV	VE			
Endpoint	**n/N**	**n/N**	**%**	**LL**	**UL**	**P-value**
Associated with HPV-16/18						
Incident infection*	***240 / 7346***	***1054 / 7320***	***78.4***	***74.9***	***81.4***	<0.0001
	~~263 / 7346~~	~~1074 / 7320~~	~~76.7~~	~~73.2~~	~~79.9~~	
Persistent infection (6-month)	***29 / 7177***	***488 / 7122***	***94.3***	***91.5***	***96.3***	<0.0001
	~~32 / 7177~~	~~497 / 7122~~	~~93.8~~	~~91.0~~	~~95.9~~	
Persistent infection (12-month)	***20 / 7035***	***227 / 6984***	***91.4***	***86.1***	***95.0***	<0.0001
	~~21 / 7035~~	~~233 / 6984~~	~~91.2~~	~~85.9~~	~~94.8~~	
Any cytological abnormality (ASC-US+)*	***48 / 7340***	***427 / 7312***	***89.0***	***84.9***	***92.1***	<0.0001
	~~51 / 7340~~	~~434 / 7312~~	~~88.5~~	~~84.4~~	~~91.7~~	
VIN/ValN1+*	2 / 7344	10 / 7312	80.0	0.3	98.1	0.0221
CIN1+	8 / 7344	96 / 7312	91.7	82.4	96.7	<0.0001
CIN1+ (TAA)*	2 / 7344	90 / 7312	97.8	91.4	99.8	<0.0001
CIN3+	2 / 7344	10 / 7312	80.0	0.3	98.1	0.0221
CIN3+ (TAA)*	0 / 7344	8 / 7312	100	36.4	100	0.0038
Associated with HPV-16						
Incident infection*	***120 / 6304***	***676 / 6172***	***83.2***	***79.4***	***86.5***	<0.0001
	~~139 / 6304~~	~~687 / 6172~~	~~80.9~~	~~76.8~~	~~84.4~~	
Persistent infection (6-month)	***22 / 6163***	***337 / 6018***	***93.8***	***90.2***	***96.3***	<0.0001
	~~23 / 6163~~	~~345 / 6018~~	~~93.7~~	~~90.1~~	~~96.1~~	
Persistent infection (12-month)	***17 / 6052***	***171 / 5903***	***90.4***	***83.8***	***94.7***	<0.0001
	~~18 / 6052~~	~~175 / 5903~~	~~90.1~~	~~83.5~~	~~94.4~~	
Any cytological abnormality (ASC-US+)*	***29 / 6299***	***275 / 6165***	***89.8***	***84.7***	***93.4***	<0.0001
	~~33 / 6299~~	~~279 / 6165~~	~~88.6~~	~~83.3~~	~~92.4~~	
VIN/ValN1+*	2 / 6303	6 / 6165	67.2	-97.0	97.2	0.1749
CIN1+	5 / 6303	70 / 6165	93.0	82.2	97.9	<0.0001
CIN1+ (TAA)*	1 / 6303	66 / 6165	98.5	91.0	100	<0.0001
CIN3+	2 / 6303	6 / 6165	67.2	-97.1	97.2	0.1749
CIN3+ (TAA)*	0 / 6303	6 / 6165	100	8.8	100	0.0146
Associated with HPV-18						
Incident infection*	***126 / 6796***	***497 / 6751***	***75.4***	***69.7***	***80.1***	<0.0001
	~~134 / 6796~~	~~509 / 6751~~	~~74.4~~	~~68.7~~	~~79.3~~	
Persistent infection (6-month)	***7 / 6642***	***184 / 6567***	***96.3***	***91.9***	***98.6***	<0.0001
	~~9 / 6642~~	~~188 / 6567~~	~~95.3~~	~~90.7~~	~~98.0~~	
Persistent infection (12-month)	***3 / 6508***	***66 / 6440***	***95.5***	***85.7***	***99.2***	<0.0001
	~~3 / 6508~~	~~70 / 6440~~	~~95.8~~	~~86.6~~	~~99.2~~	
Any cytological abnormality (ASC-US+)*	***19 / 6790***	***201 / 6746***	***90.7***	***84.7***	***94.7***	<0.0001
	~~20 / 6790~~	~~204 / 6746~~	~~90.3~~	~~84.4~~	~~94.4~~	
VIN/ValN1+*	0 / 6794	4 / 6746	100	-67.0	100	0.0616
CIN1+	3 / 6794	31 / 6746	90.4	67.7	98.3	<0.0001
CIN1+ (TAA)*	1 / 6794	29 / 6746	96.6	78.1	99.9	<0.0001
CIN3+	0 / 6794	5 / 6746	100	-19.3	100	0.0307
CIN3+ (TAA)*	0 / 6794	3 / 6746	100	-170.5	100	0.1236

Note: Exploratory endpoints are ***indicated with an asterisk***, HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots) HAV = Hepatitis A vaccine (three lots), ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC, CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC, CIN3+ = CIN3, AIS or ICC; TAA = type assignment algorithm; N = number of subjects included in each group, n = number of subjects reporting at least one event in each group Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for HPV-16 or HPV-18, VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits, P-value = Two-sided Fisher Exact test

Note: No clinically relevant change in interpretation of results.

Table 36: Summary of vaccine efficacy against virological and histopathological endpoints associated with HPV-16/18 in subjects HPV DNA negative overall and seropositive at baseline (ATP cohort for efficacy)

	HPV	HAV	VE			
Endpoint	n/N	n/N	%	LL	UL	P-value
Associated with HPV-16/18 in HPV DNA negative subjects at baseline regardless of initial serostatus						
*Incident infection**	*293 / 7815* ~~324 / 7815~~	*1177 / 7775* ~~1207 / 7775~~	*76.4* ~~74.6~~	*73.0* ~~71.1~~	*79.5* ~~77.7~~	<0.0001
Persistent infection (6-month)	*37 / 7619* ~~41 / 7619~~	*540 / 7556* ~~549 / 7556~~	*93.4* ~~92.8~~	*90.7* ~~90.0~~	*95.5* ~~95.0~~	<0.0001
Persistent infection (12-month)	*21 / 7466* ~~23 / 7466~~	*252 / 7404* ~~258 / 7404~~	*91.9* ~~91.3~~	*87.0* ~~86.4~~	*95.2* ~~94.7~~	<0.0001
*Any cytological abnormality (ASC-US+)**	*56 / 7809* ~~62 / 7809~~	*469 / 7767* ~~476 / 7767~~	*88.3* ~~87.3~~	*84.4* ~~83.2~~	*91.5* ~~90.5~~	<0.0001
VIN/ValN1+*	2 / 7814	11 / 7767	81.9	11.8	98.3	0.0127
CIN1+	12 / 7814	111 / 7767	89.3	79.9	94.8	<0.0001
CIN1+ (TAA)*	2 / 7814	103 / 7767	98.1	92.5	99.8	<0.0001
CIN2+	6 / 7814	65 / 7767	90.8	78.1	96.9	<0.0001
CIN2+ (TAA)*	1 / 7814	61/ 7767	98.4	90.0	100	<0.0001
CIN3+	2 / 7814	13 / 7767	84.6	28.2	98.5	0.0041
CIN3+ (TAA)*	0 / 7814	11 / 7767	100	57.0	100	0.0005
Associated with HPV-16/18 in HPV DNA negative and seropositive subjects at baseline						
*Incident infection**	*53 / 1509* ~~61 / 1509~~	*123 / 1551* ~~133 / 1551~~	*56.4* ~~53.7~~	*38.4* ~~35.8~~	*69.6* ~~66.9~~	<0.0001
Persistent infection (6-month)	*8 / 1462* ~~9 / 1462~~	*47 / 1496* ~~47 / 1496~~	*82.8* ~~80.6~~	*61.9* ~~58.6~~	*93.3* ~~92.0~~	<0.0001
Persistent infection (12-month)	*1 / 1427* ~~2 / 1427~~	*24 / 1461* ~~24 / 1461~~	*95.8* ~~91.5~~	*72.4* ~~64.0~~	*99.9* ~~99.2~~	<0.0001
*Any cytological abnormality (ASC-US+)**	*8 / 1509* ~~11 / 1509~~	*39 / 1547* ~~40 / 1547~~	*79.1* ~~72.0~~	*53.0* ~~42.6~~	*92.0* ~~87.6~~	<0.0001
VIN/ValN1+*	0 / 1510	1 / 1547	100	-5070.4	100	1.0000
CIN1+	4 / 1510	12 / 1547	65.8	-18.8	92.6	0.0764
CIN1+ (TAA)*	0 / 1510	10 / 1547	100	50.6	100	0.0019
CIN2+	2 / 1510	6 / 1547	65.8	-105.7	97.1	0.2887
CIN2+ (TAA)*	0 / 1510	5 / 1547	100	-22.9	100	0.0624

Note: Exploratory endpoints are ***indicated with an asterisk***, HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots) HAV = Hepatitis A vaccine (three lots), ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC, CIN3+ = CIN3, AIS or ICC; TAA = HPV type assignment algorithm; N = number of subjects included in each group, n = number of subjects reporting at least one event in each group; Subjects with an event were DNA negative at Month 0 and Month 6 and seronegative at Month 0 for the corresponding HPV type. VE (%) = Vaccine Efficacy (Conditional Method), LL, UL = 96.1% Lower and Upper confidence limits, P-value = Two-sided Fisher Exact test

Note: No clinically relevant change in interpretation of results.

Table 37: Summary vaccine efficacy against virological and histopathological endpoints associated with oncogenic HPV types in HPV DNA negative subjects at baseline (ATP cohort for efficacy)

	HPV	HAV	VE			
Endpoint	n / N	n / N	%	LL	UL	P-value
Associated with HR-HPV						
*Incident infection**	*2682 / 7864*	*3076 / 7861*	*15.3*	*10.5*	*19.8*	<0.0001
	~~2746 / 7864~~	~~3119 / 7861~~	~~14.5~~	~~9.7~~	~~19.0~~	
Persistent infection (6-month)	*1233 / 7665*	*1607 / 7640*	*25.3*	*19.2*	*31.0*	<0.0001
	~~1271 / 7665~~	~~1647 / 7640~~	~~25.0~~	~~18.9~~	~~30.6~~	
*Persistent infection (12-month)**	*549 / 7509*	*760 / 7488*	*28.9*	*20.1*	*36.8*	<0.0001
	~~585 / 7509~~	~~803 / 7488~~	~~28.4~~	~~19.8~~	~~36.1~~	
*Any cytological abnormality (ASC-US+)**	*934 / 7858*	*1191 / 7853*	*22.3*	*14.9*	*29.1*	<0.0001
	~~953 / 7858~~	~~1212 / 7853~~	~~22.1~~	~~14.8~~	~~28.9~~	
VIN/VaIN1+*	14 / 7863	32 / 7853	56.1	12.7	79.2	0.0078
CIN1+	151 / 7863	279 / 7853	45.9	33.1	56.4	<0.0001
*CIN1+ (TAA)**	134 / 7863	*261 / 7853*	*48.7*	*35.9*	*59.1*	<0.0001
		~~262 / 7853~~	~~48.9~~	~~36.1~~	~~59.3~~	
CIN2+	54 / 7863	142 / 7853	61.9	46.7	73.2	<0.0001
*CIN2+ (TAA)**	46 / 7863	*130 / 7853*	*64.6*	*49.2*	*75.7*	<0.0001
		~~131 / 7853~~	~~64.8~~	~~49.6~~	~~75.9~~	
Associated with HRW-HPV						
*Incident infection**	*2566 / 7864*	*2792 / 7861*	*9.1*	*3.8*	*14.2*	*0.0001*
	~~2624 / 7864~~	~~2846 / 7861~~	~~9.0~~	~~3.7~~	~~13.9~~	~~0.0002~~
Persistent infection (6-month)	*1207 / 7665*	*1351 / 7640*	*11.3*	*3.7*	*18.3*	*0.0013*
	~~1247 / 7665~~	~~1406 / 7640~~	~~12.1~~	~~4.7~~	~~19.0~~	~~0.0005~~
*Persistent infection (12-month)**	*532 / 7509*	*596 / 7488*	*10.9*	*-0.9*	*21.4*	*0.0441*
	~~567 / 7509~~	~~634 / 7488~~	~~12.1~~	~~0.9~~	~~22.1~~	~~0.0209~~
*Any cytological abnormality (ASC-US+)**	*912 / 7858*	*1063 / 7853*	*14.5*	*6.0*	*22.2*	*0.0003*
	~~931 / 7858~~	~~1094 / 7853~~	~~15.3~~	~~7.0~~	~~22.8~~	~~0.0001~~
VIN/VaIN1+*	13 / 7863	25 / 7853	47.8	-9.6	76.4	0.0528
CIN1+	146 / 7863	233 / 7853	37.3	21.7	49.9	<0.0001
*CIN1+ (TAA)**	133 / 7863	*213 / 7853*	*37.5*	*21.1*	*50.6*	<0.0001
		~~215 / 7853~~	~~38.0~~	~~21.9~~	~~51.1~~	
CIN2+	50 / 7863	109 / 7853	54.0	34.0	68.4	<0.0001
*CIN2+ (TAA)**	45 / 7863	*98 / 7853*	*53.9*	*32.6*	*69.0*	<0.0001
		~~99 / 7853~~	~~54.4~~	~~33.3~~	~~69.3~~	

HR-HPV = High-risk (oncogenic) HPV types i.e. HPV- 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. HRW-HPV = High risk (oncogenic) HPV types without HPV 16 and 18 i.e. HPV- 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Note: Minor change in confidence intervals and associated probability for HRW-HPV>Persistent infection>12 months.

Note: Minor change in confidence intervals and associated probability for VIN/VaIN1+.

Table 38: Summary of vaccine efficacy against 6-month persistent infection and CIN2+ associated with oncogenic HPV types in HPV DNA negative subjects at baseline

	6-month persistent infection				CIN2+			
Endpoint	**nHPV/nHAV**	**VE %**	**LL**	**UL**	**nHPV/nHAV**	**VE %**	**LL**	**UL**
Associated with HPV-31								
ATP	~~46/215~~ ***45/199***	~~78.7*~~ ***77.5****	~~70.2~~ ***68.3***	~~85.2~~ ***84.4***	2/25	92.0*	66.0	99.2
TVC-1	~~94/283~~ ***93/264***	~~66.9*~~ ***64.9****	~~57.6~~ ***54.8***	~~74.4~~ ***72.9***	11/34	67.4*	32.0	85.7
Associated with HPV-33								
ATP	~~67/123~~ ***55/100***	~~45.7*~~ ***45.1****	~~25.1~~ ***21.7***	~~60.9~~ ***61.9***	12/25	51.9	-2.9	78.9
TVC-1	~~96/166~~ ***83/142***	~~42.2*~~ ***41.6****	~~24.3~~ ***21.8***	~~56.1~~ ***56.6***	16/32	49.8*	2.9	75.2
Associated with HPV-35								
ATP	~~56/46~~ ***55/43***	~~-22.2~~ ***-28.4***	~~-88.5~~ ***-100.3***	~~20.4~~ ***17.2***	1/6	83.3	-49.1	99.7
TVC-1	~~77/67~~ ***76/64***	~~-15.4~~ ***-19.2***	~~-65.4~~ ***-72.0***	~~19.3~~ ***17.1***	1/10	90.0*	24.6	99.8
Associated with HPV-39								
ATP	147/149	1.0	-26.7	22.7	3/10	69.8	-24.2	95.2
TVC-1	204/216	5.2	-16.5	22.9	7/11	36.0	-90.1	80.1
Associated with HPV-45								
ATP	~~23/94~~ ***19/79***	~~75.7*~~ ***76.1****	~~60.4~~ ***59.1***	~~85.7~~ ***86.7***	0/4	100	-67.8	100
TVC-1	~~35/123~~ ***30/107***	~~71.6*~~ ***72.0****	~~57.6~~ ***56.9***	~~81.5~~ ***82.4***	0/5	100	-20.2	100
Associated with HPV-51								
ATP	304/354	14.5	-0.8	27.4	10/27	62.9*	18.0	84.7
TVC-1	401/475	15.8*	3.0	27.0	12/39	69.2*	38.0	85.9
Associated with HPV-52								
ATP	~~314/339~~ ***293/315***	~~7.8~~ ***7.4***	~~-8.7~~ ***-9.9***	~~21.8~~ ***22.0***	12/14	14.3	-108.1	65.4
TVC-1	~~410/458~~ ***386/434***	~~10.6~~ ***11.2***	~~-3.1~~ ***-2.9***	~~22.5~~ ***23.3***	17/17	-0.4	-117.1	53.6
Associated with HPV-56								
ATP	182/174	-5.0	-31.5	16.1	4/10	59.9	-47.1	91.5
TVC-1	225/229	1.5	-20.2	19.2	5/13	61.4	-21.2	90.0
Associated with HPV-58								
ATP	~~144/147~~ ***111/101***	~~1.8~~ ***-10.3***	~~-26.0~~ ***-48.0***	~~23.4~~ ***17.7***	6/17	64.5*	1.5	89.2
TVC-1	~~182/184~~ ***145/135***	~~0.5~~ ***-8.1***	~~-24.1~~ ***-39.4***	~~20.3~~ ***16.1***	10/20	49.6	-17.1	79.9
Associated with HPV-59								
ATP	~~97/111~~ ***56/59***	~~12.4~~ ***4.8***	~~-17.8~~ ***-42.4***	~~34.9~~ ***36.4***	1/4	74.9	-178.6	99.6
TVC-1	~~129/134~~ ***80/78***	~~3.4~~ ***-3.0***	~~-25.6~~ ***-44.9***	~~25.7~~ ***26.8***	3/5	39.7	-234.7	91.5
Associated with HPV-66								
ATP	168/178	5.7	-18.4	24.9	4/10	60.0	-46.7	91.6
TVC-1	213/221	3.7	-18.0	21.4	4/12	66.7	-15.8	92.8
Associated with HPV-68								
ATP	138/134	-3.1	-33.4	20.3	5/11	54.4	-49.8	88.4
TVC-1	185/188	1.4	-22.8	20.8	7/15	53.2	-27.6	84.7

Statistically significant results are ***indicated with an asterisk***. nHPV/nHAV = number of cases in the HPV group / number of cases in the HAV group; HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots); HAV = Hepatitis A vaccine (three lots); ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC; CIN1+ = CIN1, CIN2, CIN3, AIS or invasive cervical cancer , CIN2+ = CIN2, CIN3, AIS or invasive cervical cancer; Subjects with an event were DNA negative for the corresponding HPV type at Month 0 and Month 6 in the ATP cohort for efficacy and at Month 0 in TVC-1; VE (%) = Vaccine Efficacy (Conditional Method); LL, UL = 96.1% Lower and Upper confidence limits.

Note: MPTS PCR covers HPV types 16, 18, 31, 33, 35, 45, 52, 58 and 59.

The following results are provided for completion.

Table 39: Summary of vaccine efficacy against CIN2+, CIN1+, ASC-US+ and VIN/VaIN1+ irrespective of the HPV types in the lesion, stratified by HPV DNA status at baseline (TVC-1)

	HPV	HAV	VE			
Endpoint	**n/N**	**n/N**	**%**	**LL**	**UL**	**P-value**
In subjects irrespective of HPV DNA at baseline						
CIN2+	204/8610	296/8630	30.9	16.4	43.0	<0.0001
CIN1+	422/8610	549/8630	23.0	11.8	32.8	<0.0001
ASC-US+	1951/8610	2185/8630	11.2	5.3	16.8	<0.0001
VIN/VaIN1+	39/8610	53/8630	26.1	-16.3	53.5	0.1739
In subjects negative for oncogenic HPV types at baseline						
CIN2+	51/6893	142/6962	63.8	49.0	74.7	<0.0001
CIN1+	157/6893	278/6962	43.1	29.9	54.0	<0.0001
ASC-US+	1173/6893	1397/6962	16.0	8.8	22.6	<0.0001
VIN/VaIN1+	18/6893	34/6962	46.5	-0.3	72.5	0.0363
In subjects negative for all HPV types at baseline						
CIN2+	47/6565	132/6651	64.0	48.6	75.3	<0.0001
CIN1+	136/6565	259/6651	47.0	33.9	57.8	<0.0001
ASC-US+	1058/6565	1298/6651	18.3	11.0	25.1	<0.0001
VIN/VaIN1+	18/6565	31/6651	41.2	-11.7	70.0	0.0852

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots)
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC, CIN2+ = CIN2, CIN3, AIS or ICC, ASC-US+ = ASC-US, LSIL, HSIL, ASC-H and AGC, 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, P-value = Two-sided Fisher Exact test

Table 40: Vaccine efficacy against histopathological lesions associated with HPV-16/18 in HPV DNA positive subjects at baseline (TVC-1)

	HPV	HAV	VE			
Endpoint	**n/N**	**n/N**	**%**	**LL**	**UL**	**P-value**
HPV DNA positive and seronegative subjects at baseline						
CIN2+	18/303	27/285	37.8	-20.9	68.8	0.1216
CIN1+	27/303	36/285	30.5	-20.9	60.5	0.1819
HPV DNA positive and seropositive subjects at baseline						
CIN2+	43/315	31/290	-32.5	-123.1	20.4	0.3205
CIN1+	44/315	40/290	-3.0	-66.0	35.9	1.0000
HPV DNA positive subjects at baseline, regardless of initial serostatus						
CIN2+	62/617	58/567	0.5	-47.7	32.9	0.9235
CIN1+	72/617	76/567	13.0	-23.8	38.9	0.3801

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots)
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,
P-value = Two-sided Fisher Exact test

Table 41: Summary of safety data

Percentage of subjects with at least one event (Total Vaccinated cohort)						
	HPV			**HAV**		
		95% CI			**95% CI**	
	%	**LL**	**UL**	**%**	**LL**	**UL**
Unsolicited symptoms (day 0-29)*	42.5	40.8	44.3	43.6	41.9	45.3
Serious adverse events	7.5	7.0	8.1	7.5	7.0	8.0
Medically significant conditions	31.8	30.8	32.7	32.4	31.5	33.4
New Onset Chronic Diseases**	2.7	2.4	3.0	2.9	2.5	3.2
New Onset Autoimmune Diseases	0.8	0.7	1.0	0.8	0.7	1.0

HPV = HPV-16/18 L1 VLP AS04 vaccine (three lots), HAV = Hepatitis A vaccine (three lots)
%= percentage of subjects reporting at least once the symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
* Unsolicited symptoms were reported during the 30-day post-vaccination period by subjects included in the safety diary card subset (based on Interim Total Vaccinated cohort). All other events were reported during the entire follow-up period (based on Final Total Vaccinated cohort).
** GSK assessment

Evaluator's comment

- The explanation for reanalysis is plausible and does not materially change the interpretation of results. The conclusions and recommendations made in the CER1 are supported in this addendum as well.
- The primary variable – protection from development of precancerous cervical lesions (CIN2+) associated with HPV 16/18 in previously unexposed (naive) women aged 15-25 years was validated in this large study with demonstration of Vaccine Efficacy (VE) for Cervarix of 92.9% [96.1% CI 79.9 to 98.3%] $p < 0.0001$ using ATP cohort for efficacy (Table 31).
- The follow-up experience was based on 7344 woman (17689 PY) in HPV group compared with 7312 woman (17663 PY) in the control group. This amounts an average of 2.4 years follow-up per person. The number of subjects remaining under observation declined rapidly beyond 30-36 months (Figure 5).
- The primary analysis of ATP data was supported by results in the TVC-1 set; VE 94.5% [96.1% CI 86.2 to 98.4%], $p < 0.0001$ (Table 32).
- The protective efficacy against HPV-16/18 associated CIN3+ lesions, which denote more definitive risk of progression to invasive disease, was 90.9% [96.1% CI 60.8 to 99.1%) $p < 0.0001$ using the TVC-1 population (Table 34).
- HPV-TAA was an exploratory analysis. The interpretation was not altered following the reanalysis and supported the primary results.
- A number of secondary analyses were altered but the changes were small and did not alter the direction of effect. All results supported the protective efficacy of the vaccine with respect to vaccine type HPV-16/18 (Table 35 in unexposed subjects at baseline; Table 36 in previously exposed subjects) and overall oncogenic HPV types (Tables 37-38).
- The cross-protection against individual non-vaccine oncogenic HPV types points to a potential protective effect. However, firm conclusions are not possible due to low power with wide confidence intervals, multiplicity of comparisons and lack of advance hypothesis. The results may be used to update the clinical trials section of the PI but a definitive recommendation to allow modification of indication is not supported. The long term concerns about the potential for substitution by non-dominant HPV types and change in overall epidemiological distribution of disease cannot be ascertained from this trial and will require ongoing monitoring of data from relevant registries.
- The overall VE against CIN2+ irrespective of HPV type in the lesion in subjects regardless of HPV DNA at baseline (representing the diverse and unselected population of young woman included in this trial) was 30.9% [96.1% CI 16.4 to 43.0%] $p < 0.0001$ (Table 39).
- The subgroup analyses demonstrated lower VE in women exposed to HPV 16/18 types prior to vaccination (Table 40). Furthermore, a clinically significant detrimental effect cannot be ruled out based on these data, for example CIN+2 outcomes in women with seropositive/DNA positive status at baseline, the VE was -33% [96.1% CI -123% to 20%] $p = 0.32$.
- Whereas ongoing monitoring is required, it is proposed that the results be included in the PI for information of the prescribers. The inclusion of results in tabular format such as Table 10 is considered appropriate.

- The safety data were unaffected by the current reanalysis.
- It may be noted that the End of Study report is currently being finalised by the sponsor. It may be worthwhile to be able to access this report before finalisation of this submission.

Evaluator's recommendation

The evaluator supports update of the product information document for Cervarix with respect to the clinical trials data. The evaluator does not recommend modification of the therapeutic indication to include non-vaccine HPV types. The currently approved therapeutic indication should be retained as follows:

> *Cervarix is indicated in females from 10 to 45 years of age for the prevention of cervical cancer by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3) caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations.*

For full evaluation of the dossier, please see the accompanying CER1 to which this report serves as an addendum. The observations and recommendations in CER1 are supported.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "List of Questions" to the sponsor is generated.

There were no questions listed by the clinical evaluators.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no quality data submitted with this application.

Nonclinical

There were no nonclinical data submitted with this application.

Clinical

This submission for extension of indications was supported by an event triggered Final Analysis for Study HPV-008. Study HPV-008 is a randomised, double-blind, controlled trial designed to evaluate the efficacy of HPV-16/18 Virus Like Particle AS04-adjuvanted vaccine (Cervarix) for protection against HPV-16/18 associated CIN2+ lesions associated with HPV-16/18. The study enrolled and vaccinated 18,644 women aged 15-25 years. Enrolment commenced in 2004 and the last study visit occurred in November 2009.

Three efficacy analyses had been specified in the protocol for this study as follows:

I. An event-triggered Interim Analysis when at least 23 HPV-16/18 associated CIN2+ cases had been accrued in the Total Vaccinated Cohort of Efficacy (TVC-1). The interim analysis has been submitted and evaluated by TGA and supported the registration of Cervarix in 2007.

II. An event-triggered Final Analysis when at least 36 HPV-16/18 associated CIN2+ cases had been accrued in the According-to-Protocol Cohort of Efficacy (ATP). The required number of cases were reached in 2008 and this report was included as part of the current submission.

III. The End of Study (completion of all follow-up) analysis was triggered in March 2010 and is currently ongoing.

Towards the end of the evaluation of the Final Analysis report, GSK informed TGA of discrepancies between the Final Analysis report and the ongoing End of Study (completion of all follow-up) analysis for HPV-008. Inaccuracies in the Final Analysis report were identified in relation to virological endpoints (HPV-DNA in cervical samples). Virological endpoints at the time of Final Analysis (FA) were to be assigned on the protocol-specified PCR algorithm (LiPA followed by type-specific PCR for HPV-16 and HPV-18), but the FA also incorporated the results of an exploratory PCR called Multiplex Type Specific PCR (MPTS-PCR) which had been tested in a subset of participants. The MPTS-PCR is being developed as a more sensitive type-specific PCR for detection of nine HPV types (16, 18, 31, 33, 35, 45, 52, 58 and 59). The testing was in accordance with the study protocol as part of validation of MPTS-PCR methodology. The error led to an overestimation of a number of virological endpoints associated with the nine HPV types targeted by the MPTS-PCR in the FA.

Clinical Evaluation Report 1 (CER 1) has been completed based on the Final Analysis Report submitted in September 2009 with the report noting some uncertainties relating to virological endpoints in cervical samples in Study HPV-008.

GSK have submitted a report reanalysing the Final Analysis to address the MPTS-PCR inaccuracy as supplementary data.

Clinical Evaluation Report 2 (CER2) was prepared as an addendum to CER1 presenting the results following reanalysis of virological endpoints in Study HPV-008.

Study HPV-007 is a long-term follow-up study of a primary efficacy, immunogenicity and safety study (HPV-001) of Cervarix administered to women 15 to 25 years of age. **Study HPV-007 (Month 36) report** of efficacy and immunogenicity outcomes are presented in CER1. The month 36 report is the final analysis of HPV-007, and follows Month 12 and Month 24 interim reports. A total of 776 subjects were enrolled in HPV-007, 393 who received HPV 16/18 L1/AS04 vaccine and 383 who received placebo. Overall 700 subjects completed the study. The mean period of follow-up from the start of HPV-001 to end of HPV-007 was 5.9 years, with a maximum duration 6.4 years. Significant long term vaccine efficacy was observed against all virological, cytological and histopathological endpoints related to HPV-16 and HPV-18 infection to approximately 6 years after vaccination, which extends the previous vaccine efficacy conclusions. Up to 76 months post vaccination, 98.6% of subjects remained seropositive for HPV-16 and HPV-18 as measured by ELISA. GMTs did not show significant decline between Month 18 and Month 76 post vaccination. Safety in HPV-007 is discussed in CER 1. SAE were reported in 31 subjects in the vaccine group and 39 in the control group through the entire HPV-007 follow-up. None of the SAEs were considered related to vaccination. No deaths were reported. The incidence of SAE was 7.9% in vaccine group compared to 10.2% in placebo group. NOCD was reported in 1.3% in vaccine group and 1.6% in placebo group. Pregnancies resulting in abnormal outcome were also lower in vaccine compared to

placebo (28.4% versus 33.3%). No new safety issues were identified from HPV-007 (Month 36) report.

Study HPV-008. Of 18,729 subjects enrolled, 18,644 were included in the total vaccinated cohort, 18525 were included in the TVC- 1 and 16162 in the ATP cohort for efficacy. Approximately 26% had evidence of current or prior HPV-16/18 infection at baseline. The mean follow-up at Final Analysis was approximately 34.9 months in the ATP cohort (starting at Dose 3) and 39.4 months in the TVC-1 cohort (starting after Dose 1). CER 1 presented efficacy results.

CER 2 commented that for protocol defined primary and secondary analyses the overall treatment effect and statistical significance remained unchanged after reanalysis. Histopathological endpoints defined by HPV-DNA detection on biopsies were not impacted hence the primary efficacy analysis was unaffected. CER 2 provided a concise summary of HPV-008 efficacy results.

CER 2 identified that inaccuracy in Final Analysis results associated with MPTS-PCR potentially impacts on:

i. Virological endpoints for the 9 HPV types covered by the MPTS-PCR (6-month and 12-month persistent infection with HPV-16/18 and 6-month persistent infection with oncogenic HPV types) and exploratory endpoints (12-month persistent infection with oncogenic HPV types and incident infection and abnormal cytology [ASCUS+] associated with HPV-16/18 or other oncogenic HPV types);
ii. Histopathological endpoints defined using the HPV Type Assignment Algorithm (TAA) in which the case is not only defined by the HPV type detected in the biopsy, but also by taking into account the HPV type in one of the two preceding cervical samples. HPV TAA is an exploratory algorithm aimed at increasing specific HPV type causal association with a CIN lesion, for multiple HPV types detected in a lesion.
iii. Immunogenicity endpoints were affected due to change in the number of subjects in the ATP cohort for immunogenicity.

CER 1 reported analysis of safety in HPV-008 based on TVC for a mean follow-up time of 40.8 months (starting after Dose 1). Serious adverse events are described in CER1. The summary of safety endpoints presented in Table 28 is unchanged from the interim cohort (Table 24).

Study HPV-042 evaluated co-administration of HPV-16/18 L1/AS04 vaccine with dTpa-IPV vaccine in females between 10 and 18 years of age. A total of 751 subjects were enrolled in this randomised, open label, multicentre study. Statistical analysis tested non-inferiority for seroprotection rates for diphtheria, tetanus and polio antibodies and GMT ratio for antibodies against PT, FHA and PRN. Non-inferiority of HPV-16 and HPV-18 seroconversion rates and GMT ratios was also assessed. Tables 22 and 23 show non-inferiority was demonstrated for all dTpa-IPV and HPV antigens between the HPV and HPV+dTpa-IPV treatment groups. The incidences of local and general adverse events after dose 1 were higher in the group who received simultaneous vaccination with dTpa-IPV and HPV-16/18 L1/AS04 compared to other groups. However, the 95% CI overlapped for all comparisons. Most solicited local symptoms were mild to moderate and resolved within 4 days. Myalgia (33.4%) and headache (29.3%) were reported more frequently in the co-administration group compared to control. Most solicited general symptoms resolved within 3-5 days. Eight subjects reported a SAE but none were considered related to vaccination. No subjects were withdrawn due to an AE. The CER

accepts the proposed PI statement for dTpa, IPV and dTpa-IPV under use with other vaccines.

CER2 Conclusions for Study HPV-008

The primary variable – protection from development of precancerous cervical lesions (CIN2+) associated with HPV 16/18 in previously unexposed (naive) women aged 15-25 years was validated in this large study with demonstration of Vaccine Efficacy (VE) for Cervarix of 92.9% [96.1% CI 79.9 to 98.3%] $p < 0.0001$ using ATP cohort for efficacy.

A number of secondary analyses were altered but the changes were small and did not alter the direction of effect. Results supported the protective efficacy of the vaccine with respect to vaccine type HPV-16/18.

The cross-protection against individual non-vaccine oncogenic HPV types points to potential protective effect. However, firm conclusions are not possible due to low power with wide confidence intervals, multiplicity of comparisons and lack of advance hypothesis. The results may be used to update the clinical trials section of the PI but a definitive recommendation to allow modification of indication is not supported. The long term concerns about the potential for substitution by non-dominant HPV types and change in overall epidemiological distribution of disease cannot be ascertained from this trial and will require ongoing monitoring of data from relevant registries.

The overall VE against CIN2+ irrespective of HPV type in the lesion in subjects regardless of HPV DNA at baseline, representing the diverse and unselected population of young woman included in this trial, was 30.9% [96.1% CI 16.4 to 43.0%] $p < 0.0001$.

The subgroup analyses demonstrated lower VE in women exposed to HPV 16/18 types prior to vaccination (Table 10). Furthermore, a clinically significant detrimental effect cannot be ruled out based on these data

Risk Management Plan (RMP)

There was no RMP submitted with this application.

Risk-Benefit Analysis

Delegate Considerations

This application is referred for ACPM consideration as both CERs recommend rejection of a proposed extension of indications that includes "prevention of persistent infection, premalignant cervical lesions and cervical cancer *caused by oncogenic human papillomaviruses*", replacing *"caused by HPV types 16 and 18"* .

The Delegate supported CER2 conclusions for Study HPV-008 as summarised above.

The Delegate proposed to reject the extension of indications to include prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomaviruses. In contrast to the convincing demonstration of efficacy in prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by human papillomavirus types 16 and 18, the proposed rejection for oncogenic human papillomaviruses is based on the inadequate demonstration of efficacy due to lack of advance hypothesis for testing, the low power with wide confidence intervals reported in the analyses presented (particularly overall VE against CIN2+ irrespective of HPV type in the lesion in subjects regardless of HPV DNA at baseline), and the multiplicity of comparisons. In addition, an End of Study report for Study HPV-008 is in preparation which may be

more reliable given the previously identified inaccuracies in the submitted Final Analysis report.

CER2 recommendations with respect to the PI were also supported.

Delegate's Proposed Action

The Delegate proposed to reject this application for Human Papillomavirus Vaccine Types 16 and 18 (recombinant, AS04 adjuvanted), Cervarix, to extend indications to:

> *Cervarix is indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomaviruses (HPV). Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations (see Precautions and Clinical Trials).*

The indication must maintain "caused by human papillomavirus types 16 and 18" as there is inadequate evidence of efficacy in prevention of persistent infection, premalignant cervical lesions and cervical cancer "caused by oncogenic human papillomaviruses".

The advice of ACPM was requested.

Summary of the Response from Sponsor

GSK's current Australian submission contained updated reports from previously evaluated Phase III clinical Studies HPV-007, HPV-008 and a new study, HPV-042 to expand clinical trial data in the Cervarix PI and extend indication. While all the amendments to the Cervarix PI based on Studies HPV-007, HPV-008 and HPV-042 are acceptable, the Delegate has recommended the rejection of the extension of indication to encompass non-vaccine oncogenic HPV types based on HPV-008 data, despite vaccine efficacy being shown at 70% and 87% for CIN2+ and CIN3+ respectively, in subjects who were naïve to HPV (no evidence of current infection, or prior infection of vaccine types). This analysis included lesions caused by any HPV type, including non-vaccine types and represents the overall vaccine efficacy, *regardless* of the HPV type causing lesions in HPV naïve subjects. These values surpass the efficacy expected if the vaccine were effective only against HPV16/18. The clinical evaluation reports and the Delegate's Overview concluded that HPV-008 results support the protective efficacy of Cervarix with respect to HPV 16/18 and point to potential cross-protective effect against individual non-vaccine oncogenic HPV types. However, rejection of the proposed indication is recommended on the grounds that firm conclusions cannot be made to support modification of the indication.
In their Pre Advisory Committee on Prescription Medicines (ACPM) response, GSK presented the clarification on HPV-008 study design and results and the protective effect seen for other oncogenic HPV types, which provide the primary reasons for the proposed indication to be approved as stated:
Proposed Indication Statement:
Cervarix is indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomaviruses (HPV). Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations (See Precautions and Clinical Trials).

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommends rejection of the submission from GlaxoSmithKline Australia Pty Ltd to register an extension of indications for human papillomavirus vaccine types 16 and 18 (recombinant, AS04 adjuvanted) (Cervarix) suspension 20 µg each of HPV-16 L1 and HPV-18 L1 proteins per 0.5 mL.
In making this recommendation, the ACPM was in agreement with the Delegate that the indication must be maintained as "caused by human papillomavirus types 16 and 18" as there was inadequate evidence of efficacy in prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomaviruses.
Although secondary analyses for efficacy against all oncogenic HPV types were pre-planned, they were only secondary; do not demonstrate efficacy against each type; the hypotheses for testing were poorly defined; and the multiplicity of analyses may have resulted in false positives.
The ACPM advised that the data submitted were suitable to be included in the PI but should also include confidence intervals.

Outcome

Based on a review of quality, safety and efficacy, TGA decided to reject part of the indications, "caused by oncogenic human papillomaviruses (HPV) and to **approve the registration** of other changes to the indications and the text of the Product Information document for Cervarix human papillomavirus vaccine types 16 and 18 [recombinant, AS04 adjuvanted] suspension for injection pre-filled syringe; and Cervarix human papillomavirus vaccine types 16 and 18 [recombinant, AS04 adjuvanted] suspension for injection vial.

The approved indications for Cervarix now read as:

> *Indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations (See Precautions and Clinical Trials).*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

CERVARIX® PRODUCT INFORMATION

Human Papillomavirus Vaccine Types 16 and 18
(Recombinant, AS04 adjuvanted)

DESCRIPTION

CERVARIX contains recombinant C-terminally truncated L1 proteins from human papillomavirus (HPV) type-16 and type-18 each assembled as virus-like particles (VLPs). The HPV-16 and HPV-18 L1 antigens are prepared by recombinant DNA technology using a Baculovirus expression system in *Trichoplusia ni* cells.

HPV-16 and HPV-18 L1 antigens in CERVARIX are adjuvanted with AS04. This AS04 adjuvant system comprises aluminium hydroxide ($Al(OH)_3$) and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL). The MPL within AS04 enhances the initiation of the immune response through the activation of innate immunity, leading to an improved cellular and humoral adaptive immune response.

Each 0.5ml dose of CERVARIX contains 20 micrograms each of HPV-16 L1 and HPV-18 L1 proteins, 0.5 milligrams of $Al(OH)_3$ and 50 micrograms of MPL. CERVARIX also contains sodium chloride (NaCl) 4.4 mg, sodium phosphate - monobasic ($NaH_2PO_4.2\ H_2O$) 624 micrograms and water for injection as excipients. CERVARIX does not contain a preservative.

PHARMACOLOGY

Epidemiological evidence confirms that persistent infection with oncogenic (high-risk) HPV types is the primary cause of cervical cancer and most precursor lesions. Persistent infection with at least one oncogenic HPV type is a necessary causal factor for pre-cancerous high-grade cervical epithelial abnormalities, for example, cervical intraepithelial neoplasia (CIN).

Invasive cervical cancer includes squamous cervical carcinoma (84%) and adenocarcinoma (16%, up to 20% in developed countries with screening programs).
HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers across all regions worldwide.

Other oncogenic HPV types (HPV-31, -33, 35, 39, -45, -51, -52, -56, -58, -59, -66, -68) can also cause cervical cancer. The 5 most common types identified in cervical cancer are HPV-16, -18, -33, -45 and -31.

Mechanism of action

CERVARIX is a recombinant vaccine prepared from VLPs of the major L1 protein of HPV types 16 and 18. Since VLPs contain no viral DNA, they cannot infect cells or reproduce. Animal studies suggest that the efficacy of VLPs is largely mediated by the development of a humoral immune response and cell-mediated immunity.

Transudation of anti-HPV IgG antibodies from the serum to the cervical mucosa is thought to be the primary mechanism of protection against persistent oncogenic HPV infection, the necessary cause of cervical cancer.

CERVARIX is adjuvanted with AS04. In clinical trials CERVARIX adjuvanted with AS04 compared to the same antigens adjuvanted with aluminium hydroxide alone showed:

- significantly higher antibody titres at least 2 fold higher (at all time points analysed up to 4 years after first dose);
- significantly higher functional antibody titres (analysed up to 4 years after first dose);
- B cell memory frequency approximately 2 fold higher (at all time points analysed up to 2 years after first dose).

CLINICAL STUDIES

Vaccine Efficacy

The efficacy of CERVARIX was assessed in 2 controlled, double-blind, randomised Phase II and III clinical studies (HPV-001/007 and HPV-008) that included a total of 19,778 women aged 15 to 25 years. Both of these studies are ongoing.

Clinical trial HPV-001/007 was a study conducted in North America and Latin America. Study entry criteria were: negative for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in cervical samples, seronegative for HPV-16 and HPV-18 antibodies and normal cytology. These characteristics are representative of a population presumed naïve to oncogenic HPV types prior to vaccination.

Clinical trial HPV-008 is an on-going study conducted in North America, Latin America, Europe, Asia Pacific and Australia. Pre-vaccination samples were collected for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) testing and serum testing for HPV-16 and HPV-18 antibodies. Women were vaccinated regardless of baseline cytology and HPV serological and DNA status. These characteristics are representative of a population which includes women with or without evidence of past and/or current HPV infection.

Subjects initially infected with a particular HPV type were not eligible for the efficacy assessment of that type.

The primary endpoints in study HPV-001/007 are incident HPV-16 and/or HPV-18 infections.

The primary endpoint in study HPV-008 is HPV-16 or HPV-18 related CIN2+.

In both studies the following endpoints were evaluated:

- CIN2+ (cervical intraepithelial neoplasia grade 2 and higher grade lesions)
- CIN1+ (cervical intraepithelial neoplasia grade 1 and higher grade lesions)
- Cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) and ASC-US of suspected high grade (ASC-H).
- 12 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over a minimum interval of 10 months)
- 6 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over a minimum interval of 5 months).

In study HPV-008, the following endpoints were also evaluated:

- CIN3+ (cervical intraepithelial neoplasia grade 3 and higher grade lesions)
- VIN1+ (vulvar intraepithelial neoplasia grade 1 and higher grade lesions)
- VaIN1+ (vaginal intraepithelial neoplasia grade 1 and higher grade lesions)

Cervical intraepithelial neoplasia (CIN) grade 2 and 3 (CIN2+) was used in the clinical trials as a surrogate marker for cervical cancer. Persistent infection that lasts for at least 6 month has also been shown to be a relevant surrogate marker for cervical cancer. Although CIN1 is not a surrogate marker for cervical cancer, these lesions require medical follow-up.

1. Study HPV-001/007 – Vaccine efficacy against HPV-16/18 in women naïve to oncogenic HPV types

Efficacy results for the endpoints associated with HPV-16 and/or HPV-18 (HPV-16/18) observed in study HPV-001/007 through 6.4 years after the first vaccine dose are presented in Table 1.

Table 1: Vaccine efficacy results from Study HPV 001/007 associated with HPV-16/18

Endpoint	Cervarix n/N	Control (Al hydroxide) n/N	% Efficacy	95% CI
Incident Infection*	4/401	70/372	95.3	87.4;98.7
6 month persistent infection*	0/401	34/372	100.0	90.0;100.0

12 month persistent infection*	0/401	20/372	100.0	81.8;100.0
ASC-US**	1/505	31/497	97.3	83.6;99.9
CIN1+**	0/481	15/470	100.0	73.4;100.0
CIN2+**	0/481	9/470	100.0	51.3;100.0

*ATP cohort = All women in HPV-007 who received three doses of CERVARIX or placebo in HPV-001, and who were negative for high-risk HPV DNA and seronegative for HPV-16 and HPV-18 at month 0, and negative for HPV-16 and HPV-18 DNA at month 6.
** Total cohort = All women who had received at least one dose of CERVARIX or placebo in HPV-001, and who had any data available for outcome measurement in HPV-007.
N = Number of subjects in specific cohort
n = number of cases

In summary, sustained efficacy of the vaccine was demonstrated against HPV-16 and/or HPV-18 persistent infections, as well as against cytological abnormalities and histopathological lesions.
In study HPV-001/007, high efficacy of CERVARIX was maintained for up to 6.4 years (approximately 77 months) after dose one. Despite evidence of continuous exposure to HPV infections as observed in the control group, there is no evidence of waning protection in vaccinated women.

2. <u>Study HPV-008 - Vaccine efficacy in women with/without evidence of past and/or current HPV infection</u>

In study HPV-008, the primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were naïve to the respective HPV type at month 0 and month 6) and the Total Vaccinated Cohort-1 (TVC-1 cohort: including women who received at least one vaccine dose and were naïve to the respective HPV type at month 0). Both cohorts included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5%).
In addition, analyses of efficacy were performed on the broader Total Vaccinated Cohort (TVC) which included all vaccinated women.

Table 2: Population Cohorts analysed in Study HPV-008

Cohort	Abbreviation	Definition	Analysed for
According to Protocol cohort	ATP	Women who received three doses of study vaccine, complied with the study protocol, and had normal or low-grade cytology at Month 0.	Primary and secondary endpoints
Total Vaccinated Cohort -1	TVC-1	Women who received at least one dose of study vaccine and had normal or low-grade cytology at Month 0	Primary and secondary endpoints
Total Vaccinated Cohort	TVC	Women who received at least one dose of study vaccine	Supportive
Total	TVC naive	Women who received at least one dose of study	Exploratory

Vaccinated Cohort of HPV naïve women		vaccine, and had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0.	analyses

The TVC approximates a general population of women, including those who are sexually active, and may have previous or current HPV infection, cytological abnormalities or precancerous cervical lesions. The TVC-naïve cohort includes women with no evidence of previous or current HPV infection and no cytological abnormalities, and approximates to a population of young women before sexual debut.

For the three Total Vaccinated cohorts, case counting began the day after first vaccination. For the According to Protocol cohort, case counting began the day after the third vaccination.

In study HPV-008, approximately 26% of women had evidence of current and/or prior HPV-16/18 infection and less than 1% of women were HPV DNA positive for both HPV-16 and HPV-18 types at baseline. The mean follow-up for women included in study HPV-008 was approximately 39 months.

Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 are provided in Table 3.

Table 3: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 - Protocol-specified analysis

HPV-16/18 endpoint	ATP cohort[(1)]			TVC-1 cohort[(2)]		
	Cervarix (N = 7344)	Control (N = 7312)	% Efficacy (96.1% CI)	Cervarix (N = 8040)	Control (N = 8080)	% Efficacy (96.1% CI)
	n	n		n	n	
CIN2+	4	56	92.9 (79.9;98.3)	5	91	94.5 (86.2;98.4)
CIN1+	8	96	91.7 (82.4;96.7)	11	135	91.8 (84.5;96.2)

N = number of subjects included in each group
n = number of cases
(1) 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6
(2) at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0

Further investigation identified that several CIN2+ and CIN1+ cases had multiple oncogenic HPV types in the lesion. In order to distinguish between the HPV type(s) most likely to be responsible for a lesion, from the HPV type(s) only temporally associated, an HPV type assignment was applied (exploratory analysis). The HPV type assignment considered the HPV types detected by Polymerase Chain Reaction (PCR) in at least one of the two preceding cytologic samples, in addition to types detected in the lesion. Based

on this HPV type assignment, the analysis excluded CIN1+ and CIN2+ cases (in the vaccine group and in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial (see Table 4 below).

Table 4: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 - HPV type assignment

HPV-16/18 endpoint	ATP cohort[1]			TVC-1 cohort[2]		
	Cervarix (N = 7344)	Control (N = 7312)	% Efficacy (96.1% CI)	Cervarix (N = 8040)	Control (N = 8080)	% Efficacy (96.1% CI)
	n	n		n	n	
CIN2+	1	53	98.1% (88.4;100)	2	87	97.7% (91.0;99.8)
CIN1+	2	90	97.8% (91.4;99.8)	5	128	96.1% (90.3;98.8)

N = number of subjects included in each group
n = number of cases
(1) 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6
(2) at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0

In addition, statistically significant vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16 and HPV-18 individually was demonstrated for both cohorts (Table 5).

Table 5: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16 and HPV- 18 - HPV type assignment

	Vaccine Efficacy (%), 96.1% CI	
	HPV 16	**HPV 18**
CIN2+		
ATP	100 (91.0;100)	92.3 (45.7;99.9)
TVC-1	98.6 (91.5;100)	95.4 (70.1;99.9)
CIN1+		
ATP	98.5 (91.0;100)	96.6 (78.1;99.9)
TVC-1	96.8 (90.0;99.4)	95.0 (79.7;99.5)

Statistically significant efficacy against virological and cytological endpoints associated with HPV16/18 was demonstrated (Table 6).

Table 6: Vaccine efficacy against virological and cytological endpoints associated with HPV-16/18

HPV-16/18 endpoint	ATP cohort[1]			TVC-1 cohort[2]		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n/N	n/N		n/N	n/N	
Virological endpoints						
6 month persistent infection	29/7177	488/7122	94.3 (91.5;96.3)	67/7941	661/7964	90.2 (87.3;96.2)
12 month persistent infection	20/7035	227/6984	91.4 (86.1;95.0)	51/7812	340/7823	85.3 (79.9;89.4)

Cytological endpoint						
Cytological abnormalities (≥ASCUS)	48/7340	427/7312	89.0 (84.9;92.1)	75/8040	553/8080	86.7 (82.8;89.8)
N = number of subjects included in each group n = number of cases (1) 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6 (2) at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0						

Statistically significant vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was observed in the ATP cohort, 80.0% (96.1% CI: 0.3;98.1) and in the TVC-1 cohort 83.2% (96.1% CI: 20.2;98.4).

There was no evidence of protection from disease caused by the HPV types for which subjects were HPV DNA positive at study entry. However, individuals already infected with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other vaccine HPV type.

Prophylactic Efficacy against oncogenic HPV genotypes other than HPV-16 and HPV-18

HPV-16 and HPV-18 are not responsible for all cervical cancers. Other oncogenic HPV types can also cause cervical cancer. Of these, HPV-45, HPV-31 and HPV-33 are the next most prevalent types worldwide. Study HPV-008 assessed persistent infection with the following oncogenic HPV types by PCR; HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 as a secondary endpoint. Recent studies have shown a strong association between persistent infection with oncogenic HPV and high grade abnormalities (CIN2/CIN3).

High levels of vaccine efficacy for both the virological and histopathological endpoints were also seen for the other HPV oncogenic types. Statistical significance was seen for the 3 most prevalent (after HPV 16 and HPV 18) HPV types 31, 33 and 45 for the 6 month and 12 month persistent infections.

The vaccine efficacy results for the various cohorts studied for the three most prevalent HPV types after HPV types 16 and 18 are provided in Table 7.

Table 7: Vaccine efficacy results from Study HPV-008 against non-vaccine oncogenic HPV types

	Vaccine Efficacy (%) 96.1% CI		
	HPV 31	**HPV 33**	**HPV 45**
CIN2+			
ATP	92.0 66.0;99.2	51.9 -2.9;78.9	100 -67.8;100
TVC1	67.4 32.0;85.7	49.8 2.9;75.2	100 -20.2;100
TVC naive	100	72.3	100

	78.3;100	19.1;92.5	-19.5;100
CIN1+			
ATP	87.7 70.2;95.9	38.1 -13.0;66.9	91.7 39.9;99.9
TVC1	69.0 46.9;82.8	38.9 -2.3;64.2	93.3 53.8;99.9
TVC naive	90.0 66.5;98.2	62.0 7.2;86.2	90.0 25.1;99.8
Persistent infection 12 month			
ATP	80.5 66.1;89.5	41.0 -4.0;67.3	60.0 1.5;85.5
TVC1	60.6 43.6;72.9	37.0 2.5;59.8	51.4 8.3;75.3
TVC naive	70.6 46.5;84.8	31.9 -21.0;62.4	82.5 36.3;97.0
Persistent infection 6 month			
ATP	77.5 68.3;84.4	45.1 21.7;61.9	76.1 59.1;86.7
TVC1	64.9 54.8;72.9	41.6 21.8;56.6	72.0 56.9;82.4
TVC naive	75.3 62.7;84.2	41.8 13.9;61.1	82.3 63.9;92.3

Statistically significant vaccine efficacy against 6-month persistent infection, 12-month persistent infection and CIN1+ associated with HPV-45 was observed in all cohorts. In the broader Total Vaccinated Cohort (TVC), vaccine efficacy against CIN2+ associated with HPV-45 was also statistically significant with 0 cases in the vaccine group versus 6 cases in the control group [vaccine efficacy: 100% (96.1% CI: 7.0;100)].

The results for vaccine efficacy against the virological and histopathological endpoints were statistically significant for all oncogenic HPV types including HPV16/18, in HPV DNA negative subjects, regardless of initial serostatus, in the ATP cohort and are provided in Table 8.

Table 8: Vaccine efficacy associated with oncogenic HPV types in HPV DNA negative subjects at baseline, regardless of initial serostatus (ATP cohort)

Endpoint	Cervarix n/N	Control n/N	% Efficacy	96.1% CI
6 month persistent infection	1271/7665	1647/7640	25.0	18.9;30.6
12 month persistent infection	585/7509	803/7488	28.4	19.8:36.1
ASC-US	953/7858	1212/7853	22.1	14.8;28.9
CIN1+	151/7863	279/7853	45.9	33.1;56.4
CIN2+	54/7863	142/7853	61.9	46.7;73.2

Overall impact of the vaccine on HPV disease burden

The overall vaccine efficacy irrespective of HPV DNA in lesions and stratified by baseline HPV DNA status and serostatus was evaluated in study HPV-008 (see Table 9). In presumed HPV-naïve women who were HPV DNA negative for the 14 oncogenic HPV

types at baseline and in a general population of women irrespective of HPV DNA status at baseline, statistically significant vaccine efficacy against CIN2+ and CIN1+ was demonstrated in the TVC-1 cohort and in the broader TVC cohort that included all vaccinated women. Similar prophylactic efficacy was seen in women who had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0, i.e TVC naïve cohort . The impact of CERVARIX on reduction of local cervical therapy (Loop Electro-Excision Procedure, Cone, Knife or Laser) was also evaluated and was statistically significant in both cohorts.

Table 9: Overall Vaccine efficacy irrespective of HPV DNA in lesions (TVC-1, TVC naive and TVC cohorts)

			Cervarix		Control		% Efficacy (96.1% CI)
			N	***n***	***N***	***n***	
CIN2+	Prophylactic efficacy in high risk HPV DNA negative women*	***TVC-1***	6893	51	6962	142	63.8 (49.0,74.7)
		TVC naive	5449	33	5436	110	70.2 (54.7;80.9)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	***TVC-1***	8610	204	8630	296	30.9 (16.4,43.0)
		TVC	8667	224	8682	322	30.4 (16.4;42.1)
CIN1+	Prophylactic efficacy in high risk HPV DNA negative women*	***TVC-1***	6893	157	6962	278	43.1 (29.9,54.0)
		TVC naive	5449	106	5436	211	50.1 (35.9;61.4)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	***TVC-1***	8610	422	8630	549	23.0 (11.8,32.8)
		TVC	8667	451	8682	577	21.7 (10.7;31.4)
Local cervical therapy	Overall efficacy (all women irrespective of baseline HPV DNA status)	***TVC-1***	8610	162	8630	219	25.7 (7.6;40.4)
	Prophylactic efficacy in high risk HPV DNA negative women*	***TVC naive***	5449	26	5436	83	68.8 (50.0;81.2)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	***TVC***	8667	180	8682	240	24.7 (7.4;38.9)

N = number of subjects included in each group
n = number of cases
* HPV DNA negative for 14 oncogenic HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68)

Overall vaccine efficacy against CIN3+ irrespective of the HPV DNA type found in the lesion and irrespective of the subject's baseline HPV DNA and serostatus was statistically significant in both the TVC-1 cohort [with 64 cases in the vaccine group versus 103 cases in the control group (vaccine efficacy: 37.7%, CI: 12.6;55.9)] and TVC cohort [with 77 cases in the vaccine group versus 116 cases in the control group (vaccine efficacy: 33.4%, CI: 9.1;51.5)]

Immunogenicity

The antibody response to HPV-16 and HPV-18 was measured using a type specific ELISA which was shown to correlate with neutralisation assays (including pseudovirion based assay developed by the US National Cancer Institute). Due to the high efficacy of the vaccine, it has not been possible to establish minimum anti-HPV-16 and anti-HPV-18 antibody levels that protect against clinical disease caused by HPV-16 and/or 18.

The immunogenicity induced by three doses of CERVARIX has been evaluated in 5,303 female subjects from 10 to 55 years of age.

In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV type 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination.

Immunogenicity in women aged 15 to 25 years

The immune response against HPV-16 and HPV-18 was evaluated up to 76 months post dose 1, in study HPV-001/007 in women aged 15 to 25 years at the time of vaccination. Results are presented in Figures 1 and 2 below:

Figure 1: Evolution of GMT's for anti-HPV-16 IgG antibodies during studies HPV-001 and HPV-007 (ATP cohort for immunogenicity)

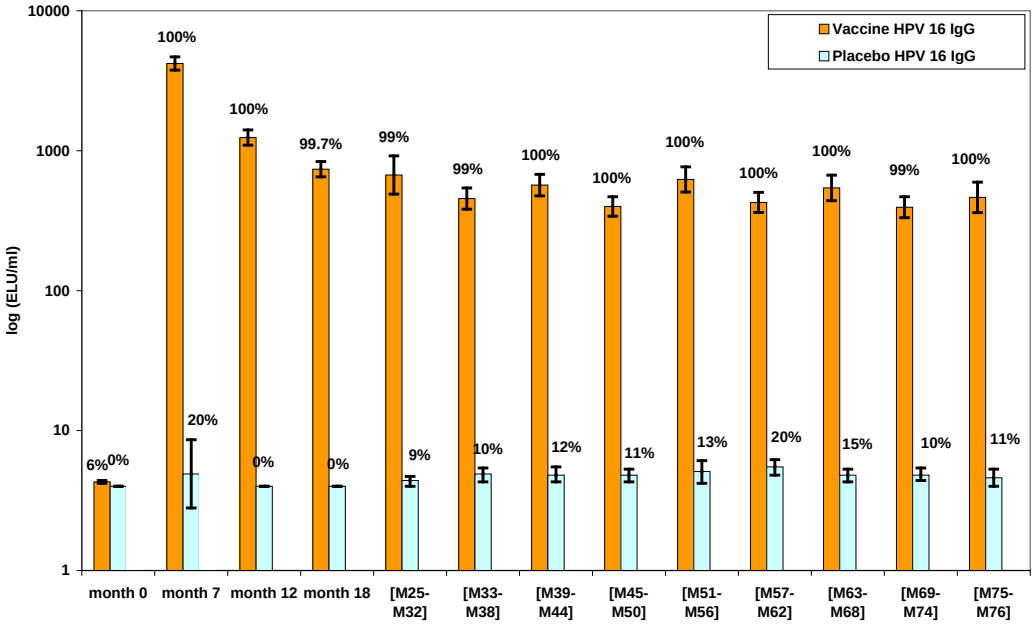
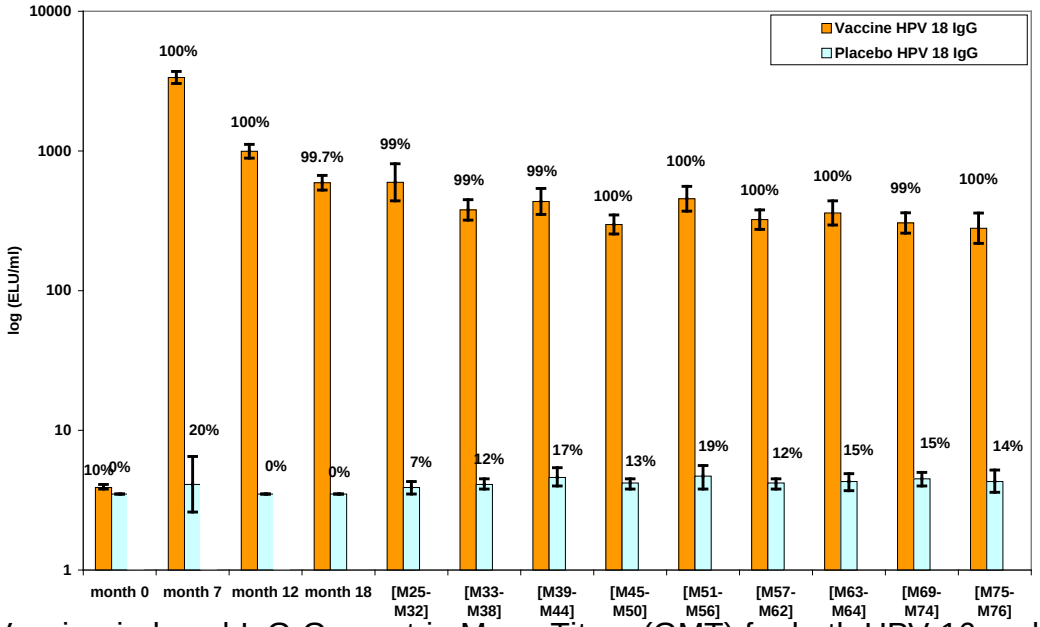


Figure 2: Evolution of GMT's for anti-HPV-18 IgG antibodies during studies HPV-001 and HPV-007 (ATP cohort for immunogenicity)



Vaccine-induced IgG Geometric Mean Titres (GMT) for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to end of the follow-up (month 76). At the end of the follow-up period, GMTs for both HPV 16 and 18 were still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection (natural infection). Nevertheless, natural infection antibody levels may not consistently protect against subsequent infections.

A similar kinetic profile was observed with the neutralising antibodies.

In study HPV-008, immunogenicity up to month 36 was similar to the response observed in study HPV-001/007.

Bridging the efficacy of CERVARIX demonstrated in 15 to 25 year olds to other age groups

In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV type 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher compared to women aged 15 to 25 years.

In a clinical study performed in women aged 26 to 55 years, after vaccination, 100% of initially seronegative subjects had seroconverted to both HPV-16 and HPV-18 antigens in all age groups (at month 7) and remained seropositive up to month 18. As observed with other vaccines, the immune response elicited by the vaccine decreases with increasing age. This is not unexpected since this reflects the senescence of the immune system. Furthermore, GMTs remained in the same range or higher as those observed in the plateau phase of the long term follow up in the efficacy study HPV-001/007 in women aged 15-25 years.

On the basis of immunogenicity data observed in females aged 10 to 14 years and aged 26 to 45 years, the efficacy of Cervarix is inferred from 10 to 45 years.

Immunogenicity in seropositive women

The vaccination of women who were initially seropositive for HPV-16 or HPV-18 or both types has shown that the presence of anti-HPV-16 and/or anti-HPV-18 antibodies from natural infection does not affect the immune response to the HPV-16/18 vaccine.

Immunogenicity in males

To date, the vaccine has not been evaluated in males.

INDICATIONS

CERVARIX is indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations (*See Precautions and Clinical Trials)*.

CONTRAINDICATIONS

CERVARIX should not be administered to subjects with known hypersensitivity to any component of the vaccine (*See Description)*.

PRECAUTIONS

As with other vaccines, the administration of CERVARIX should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As for other vaccines administered intramuscularly, CERVARIX should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

CERVARIX should under no circumstances be administered intravascularly or intradermally.

No data are available on subcutaneous administration of CERVARIX.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

CERVARIX is a prophylactic vaccine. CERVARIX is not intended to be a treatment for persistent infection or for HPV-related lesions present at the time of vaccination. CERVARIX is not intended to prevent progression of established HPV-related lesions present at the time of vaccination.

HPV-16 and HPV-18 are not responsible for all cervical cancers (*see Clinical Studies).* Other oncogenic HPV types can also cause cervical cancer. HPV infections and related clinical outcomes due to these other oncogenic types may not be prevented by vaccination.

Vaccination is primary prevention and is not a substitute for regular cytological screening (secondary prevention) or for precautions against exposure to HPV and sexually transmitted diseases.

There are no data on the use of CERVARIX in subjects with impaired immune responsiveness such as HIV infected patients or patients receiving immunosuppressive treatment. For these individuals an adequate immune response may not be elicited.

Duration of protection has not been established. Limited data support protective efficacy for 6.4 years after the first dose. Long-term studies are ongoing to establish the duration of protection.

Effects on Fertility

Fertility was not affected in female rats given double the clinical dose of CERVARIX by intramuscular administration 30 days prior to mating.

Use in Pregnancy (Category B2)

Specific studies of the vaccine in pregnant women were not conducted. Pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued in case of a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination. During prelicensure clinical development, a total of 1,737 pregnancies (n = 870 for CERVARIX) were reported. The proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion), were similar between treatment groups. Sub-analyses were conducted to describe pregnancy outcomes in 415 women (n = 210 for CERVARIX) who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose. The majority of subjects gave birth to normal infants (9.4% of pregnancies were ongoing at the time of the analysis). Apart from elective procedures, spontaneous abortion was next in frequency, reported in a total of 8.9% of subjects: 11% for CERVARIX, 5.7% for Hepatitis A Vaccine control, and 13.8% for placebo. The background rate of spontaneous abortion in individuals who are known to be pregnant has been reported to be 13-16%. These data are insufficient to recommend use of CERVARIX during pregnancy. Vaccination should therefore be postponed until after pregnancy.

The effect of CERVARIX on embryo-foetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.

No adverse effects on embryofetal development, parturition or postnatal development were observed in pregnant rats that received double the clinical dose of vaccine on 4 occasions during gestation.

Use in Lactation

CERVARIX should only be used during breast-feeding when the possible advantages outweigh the possible risks.

The effect on breastfed infants of the administration of CERVARIX to their mothers has not been evaluated in clinical studies.

Serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

Genotoxicity

The genotoxic potential of CERVARIX has not been investigated. The adjuvant substance MPL has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation and chromosomal aberration) and an *in vivo* rat micronucleus test. Under the condition of these assays, MPL did not cause genetic damage.

Carcinogenicity

The carcinogenic potential of CERVARIX has not been investigated.

Ability to perform tasks that require judgement, motor or cognitive skills

No studies on the effects on the ability to drive or use machines have been performed.

Interactions

Use with other vaccines

CERVARIX can be given concomitantly with any of the following vaccines: reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), inactivated poliovirus vaccine (IPV) and the combined dTpa-IPV vaccine. If CERVARIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Use with hormonal contraceptive

In clinical studies, approximately 60% of women who received CERVARIX used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of CERVARIX.

Use with systemic immunosuppressive medications

As with other vaccines it may be expected that in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

ADVERSE REACTIONS

In total approximately 45,000 doses of CERVARIX were administered to approximately 16,000 subjects aged 10 – 68 years. These subjects were followed to assess the safety of the vaccine.

Adverse reactions occurring after vaccination during these studies were reported. The most common reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

The following table summarises data from seven pivotal studies for solicited local and general symptoms reported during a 7-day follow-up period after vaccination.

Table10 Pooled safety analysis: Incidence of solicited local and general symptoms reporting during the 7-day (Days 0-6) post-vaccination period following all doses (Total vaccinated cohort)

		CERVARIX		ALU		HAV360		HAV720	
Symptom	**Type**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Solicited local symptoms									
Pain	All	22806	78.0	4485	52.5	3059	41.3	8750	58.9
	Grade 3	22806	6.3	4485	3.4	3059	0.8	8750	1.8
Redness (mm)	All	22806	29.6	4485	10.6	3059	13.7	8750	16.0
	>50	22806	0.6	4485	0.0	3059	0.1	8750	0.0
Swelling (mm)	All	22806	25.8	4485	8.2	3059	8.6	8750	10.1
	>50	22806	1.1	4485	0.0	3059	0.2	8750	0.2
Solicited general symptoms									
Fatigue	All	22802	33.1	4481	22.8	3058	24.6	8751	35.3
	Grade 3	22802	1.5	4481	1.2	3058	1.1	8751	1.3
Gastrointestinal symptoms	All	22802	12.9	4481	11.6	3058	11.3	8751	14.0
	Grade 3	22802	0.7	4481	0.7	3058	0.8	8751	0.7
Headache	All	22802	29.5	4481	25.9	3058	25.4	8751	30.8
	Grade 3	22802	1.6	4481	1.2	3058	1.6	8751	1.4
Arthralgia	All	21222	10.2	2916	7.6	3058	9.3	8751	8.6
	Grade 3	21222	0.4	2916	0.2	3058	0.2	8751	0.3
Myalgia	All	21222	28.1	2916	9.9	3058	17.1	8751	26.5
	Grade 3	21222	1.4	2916	0.2	3058	0.5	8751	0.6
Fever (Axillary) (°C)	All	22802	5.1	4481	5.2	3058	6.8	8751	4.6
	>39°C	22802	0.2	4481	0.2	3058	0.6	8751	0.1
Rash	All	22802	3.8	4481	2.7	3058	2.6	8751	3.6
	Grade 3	22802	0.1	4481	0.0	3058	0.1	8751	0.1

CERVARIX group (Studies HPV-001, 008 subset, -012, -013, -014, -015 subset and -016: girls and women 10 years and above)

ALU = $AI(OH)_3$ control group (Studies HPV-001 and -015 subset; adolescent girls and women 15 years and above)

HAV360 = Hepatitis A control group containing 360 EU hepatitis A antigen per dose (Study HPV-013; girls 10-14 years of age)

HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-008 subset; adolescent girls and women 15-25 years of age)

N=number of documented doses

% = percentage of doses followed by at least one type of symptom

Grade 3 Pain: Spontaneously painful (HPV-001) or Pain that prevents normal activity (HPV-008, HPV-012,

HPV-013, HPV-014, HPV-015 and HPV-016)

Other events

Other adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.
Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to ≤1/100)
Rare (≥1/10,000 to, ≤1/1,000)

Infections and infestations:
Uncommon: upper respiratory tract infection

Blood and lymphatic system disorders:
Uncommon: lymphadenopathy

Nervous system disorders:
Very common: headache
Uncommon: dizziness

Gastrointestinal disorders:
Common: gastrointestinal including nausea, vomiting, diarrhoea and abdominal pain

Skin and subcutaneous tissue disorders:
Common: itching/pruritus, rash, urticaria

Musculoskeletal and connective tissue and bone disorders:
Very common: myalgia
Common: arthralgia

General disorders and administration site conditions:
Very common: injection site reactions including pain, redness, swelling; fatigue
Common: fever (≥38°C)
Uncommon: other injection site reactions such as induration, local paraesthesia

Post Marketing Data

Immune system disorders:
Rare: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders:
Rare: syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements.

DOSAGE AND ADMINISTRATION

Dosage
The primary vaccination course consists of three doses.

The recommended vaccination schedule is 0, 1, 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 9 months after the first dose.

The necessity for a booster dose has yet to be established *(see "Clinical Studies")*.

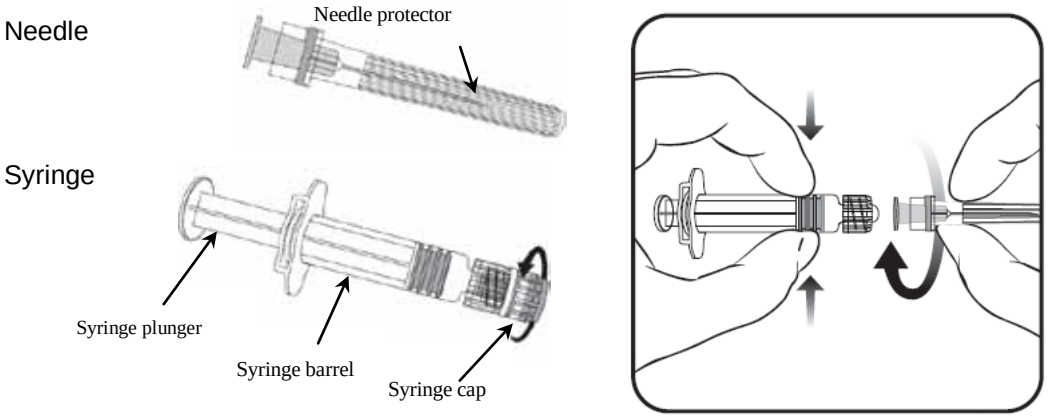
Method of administration
CERVARIX is for intramuscular injection in the deltoid region *(see "Precautions", "Drug Interactions")*.

The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

Instructions for administration of the vaccine presented in pre-filled syringe



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

CERVARIX syringe or vials are for single use in a single patient only. Any unused product of waste material should be disposed of in accordance with local requirements.

Overdosage

No case of overdose has been reported. In the event of overdosage, please contact the Poisons Information Centre on 13 11 26.

STORAGE

CERVARIX must be stored at +2°C to +8°C. DO NOT FREEZE, discard if vaccine has been frozen. The vaccine should be stored in the original package in order to protect from light.

CERVARIX should be administered as soon as possible after being removed from refrigeration. CERVARIX can be kept out of refrigeration at temperatures at or below 25°C, for a total time of not more than 72 hours or at temperatures between 25°C and 37°C, for a total time of not more than 24 hours.

The shelf life of CERVARIX is four years from the date of manufacture at temperatures of +2°C to +8°C. The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

CERVARIX is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed. This does not constitute a sign of deterioration.

CERVARIX is presented as

- 0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles in pack sizes of 1 and 10, or
- 0.5 ml of suspension in vial (type I glass) with a stopper (rubber butyl) in pack sizes of 1, 10 and 100.

Not all pack sizes may be marketed.

MANUFACTURER:

GlaxoSmithKline Biologicals s.a.

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1330 Rixensart
Belgium

DISTRIBUTED IN AUSTRALIA BY:

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