SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** GlaxoSmithKline Biologicals' human papillomavirus (HPV) next generation vaccine **Name of active substance:** HPV-16 L1 VLP protein HPV-18 L1 VLP protein HPV-33 L1 VLP protein HPV-58 L1 VLP protein	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study: A phase I/II, partially-blind, randomized multicentre study to assess the safety and immunogenicity of an HPV-16/18/33/58 L1 VLP vaccine formulated with different adjuvant systems when administered intramuscularly according to a 3-dose (0, 1, 6-month) or 2-dose schedules (0, 3-month or 0, 6-month) in healthy adult females (18-25 years of age).

Principal investigator:
This study was conducted by 3 investigators in 1 country (Belgium): Prof. [redacted] ([redacted] Prof. [redacted] and Prof. [redacted] Prof. [redacted] was acting as the principal investigator.

Study centre(s):
Multi centre: 3 study centres participated in the study: [redacted] and [redacted]

Publication (reference):
Not published as of 29 January 2010

Study period:	**Clinical phase: I/II**
Study initiation date: 25 May 2007 Study completion date: 13 October 2008	

Objectives:

Co-Primary:

Safety

- To assess the safety of the HPV-16/18/33/58 L1 VLP vaccine with respect to the incidence, intensity and relationship to vaccination of solicited local and general symptoms reported during the 7-day period (Day 0-6) following each dose of vaccine, when administered as different formulations and different schedules.

Immunogenicity

- To assess the immune response (by enzyme-linked immunosorbent assay [ELISA]) to the HPV-16 and HPV-18 components of the HPV-16/18/33/58 L1 VLP vaccine at one month after the last dose of vaccine (Month 7 or Month 4 depending on the schedule) when administered as different formulations and different schedules.

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Secondary:

Safety

- To assess the safety (except for solicited symptoms as already primary objective) of the HPV-16/18/33/58 L1 VLP vaccine up to one month after the last dose of vaccine (Month 7 or Month 4 depending on the schedule) when administered as different formulations and different schedules.
- To assess the safety of the HPV-16/18/33/58 L1 VLP vaccine during an extended safety follow-up period (from one month [Month 7 or Month 4 depending on the schedule] up to six months after the last dose of vaccine [Month 12 or Month 9 depending on the schedule]) when administered as different formulations and different schedules.

Immunogenicity

- To assess the immune response to the HPV-16 and HPV-18 components of the HPV-16/18/33/58 L1 VLP vaccine before the second dose of vaccine (Month 1, Month 3 or Month 6 depending on the schedule), at one month after the second dose of vaccine (Month 2 for groups with the 3-dose schedule only), and at six months after the last dose of vaccine (Month 12 or Month 9 depending on the schedule) when administered as different formulations and different schedules.
- To assess the immune response to the HPV-33 and HPV-58 components of the HPV-16/18/33/58 L1 VLP vaccine before the second dose of vaccine (Month 1, Month 3 or Month 6 depending on the schedule), at one month after the second dose of vaccine (Month 2 for groups with the 3-dose schedule only), and at one month (Month 7 or Month 4 depending on the schedule) and six months (Month 12 or Month 9 depending on the schedule) after the last dose of vaccine when administered as different formulations and different schedules.

Exploratory

Immunogenicity

- To assess the immune response to HPV-16, 18, 33 and 58:
  - by cell mediated immune (CMI) response at Month 0, at one month after the second dose of vaccine (Month 2 for groups with the 3-dose schedule only), at one month (Month 7 or Month 4 depending on the schedule) and six months (Month 12 or Month 9 depending on the schedule) after the last dose of vaccine in a subset of pre-selected subjects (approximately 40 subjects per group).
- To assess the cross-immune response to HPV-45, 31 and 52:
  - by antibody response at Month 0, before the second dose of vaccine (Month 1, Month 3 or Month 6 depending on the schedule), at one month after the second dose of vaccine (Month 2 for groups with the 3-dose schedule only), and at one month (Month 7 or Month 4 depending on the schedule) and six months (Month 12 or Month 9 depending on the schedule) after the last dose of vaccine in all subjects.
  - by CMI response at Month 0, at one month after the second dose of vaccine (Month 2 for groups with the 3-dose schedule only), at one month (Month 7 or Month 4 depending on the schedule) and six months (Month 12 or Month 9 depending on the schedule) after the last dose of vaccine in a subset of pre-selected subjects (approximately 40 subjects per group).

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Study design:

- Staggered design (Part A and Part B): In the first part (Part A), safety was monitored in a subset (10%) of subjects by assessing reactogenicity and biochemical/haematological parameters up to Day 7 after administration of the first dose (Interim analysis 1). If the safety evaluation did not reveal any safety concern, the remainder of the subjects (Part B) were enrolled and administered with the first dose of vaccine.
- Treatment allocation: Internet based randomisation (SBIR) (1:1:1:1:1:1).
- Blinding: partially-blind: open for schedule, observer-blind within the 3-dose schedule, and single-blind within the 2-dose schedule.
- Control: GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine: BivAS04
- Treatment Groups: Five HPV-16/18/33/58 groups and one HPV-16/18 control group:

Group	HPV-16	HPV-18	HPV-33	HPV-58	Adjuvant	Schedule
BivAS04	20 μg	20 μg			AS04	0, 1, 6
AS04016	20 μg	20 μg	20 μg	20 μg	AS04	0, 1, 6
AS1E016	20 μg	20 μg	10 μg	10 μg	AS01E	0, 1, 6
AS2W016	20 μg	20 μg	10 μg	10 μg	AS02W	0, 1, 6
AS1E03	20 μg	20 μg	10 μg	10 μg	AS01E	0, 3
AS1E06	20 μg	20 μg	10 μg	10 μg	AS01E	0, 6

BivAS04 = HPV-16, 18 AS04 (0, 1, 6)
AS04016 = HPV-16, 18, 33 (20 μg), 58 (20 μg) AS04 (0, 1, 6)
AS1E016 = HPV-16, 18, 33 (10 μg), 58 (10 μg) AS01E (0, 1, 6)
AS2W016 = HPV-16, 18, 33 (10 μg), 58 (10 μg) AS02W (0, 1, 6)
AS1E03 = HPV-16, 18, 33 (10 μg), 58 (10 μg) AS01E (0, 3)
AS1E06 = HPV-16, 18, 33 (10 μg), 58 (10 μg) AS01E (0, 6)

- Vaccination schedules:
  - HPV-16/18 L1 VLP AS04 vaccine (BivAS04), HPV-16/18/33/58 L1 VLP AS04 vaccine (AS04016), HPV-16/18/33/58 L1 VLP AS01E vaccine (AS1E016) and HPV-16/18/33/58 L1 VLP AS02W vaccine (AS2W016) groups 3 doses of vaccine administered according to a 0, 1, 6-month schedule.
  - HPV-16/18/33/58 L1 VLP AS01E (0, 3) vaccine (AS1E03) group: 2 doses administered according to a 0, 3-month schedule.
  - HPV-16/18/33/58 L1 VLP AS01E (0, 6) vaccine (AS1E06) group: 2 doses administered according to a 0, 6-month schedule.

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- Blood samples were collected according to the following time points for each dose schedule group:

Groups	Visit 1	FU Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
3-dose schedule groups	Month 0	Day 7	Month 1	Month 2	-	Month 7	Month 12
2-dose schedule group (0, 3)	Month 0	Day 7	Month 3	Month 4	Month 9	-	-
2-dose schedule group (0, 6)	Month 0	Day 7	Month 6	Month 7	Month 12	-	-

Note: Blood samples were taken from all subjects at all visits, except at follow-up (FU) Visit 1, only from the 9 first enrolled subjects of each vaccine group (54 subjects in total) a blood sample was taken for safety laboratory tests.

- For antibody response: At Visits 1, 2, 3, 5 and 6 for the 3-dose schedule groups and at Visits 1, 2, 3 and 4 for the 2-dose schedule groups.
- For B cell response: At Visits 1, 5 and 6 for the 3-dose schedule groups and at Visits 1, 3 and 4 for the 2-dose schedule groups.
- For T cell response: At Visits 1, 3 and 5 for the 3-dose schedule groups and at Visits 1 and 3 for the 2-dose schedule groups.
- For biochemical and hematological laboratory safety parameters: At Visits 1, 5 and 6 for all subjects in the 3-dose schedule groups and at Visits 1, 3 and 4 for all subjects in the 2-dose schedule groups. In addition, at FU Visit 1 (Day 7) for the first 54 subjects (9 per group).

- A cervical sample for HPV DNA testing was taken from all subjects at baseline (Month 0).
- Type of study: self-contained
- Data collection: Remote Data Entry (RDE).

This study report comprises the results of the active phase (Month 4/7 data depending on the vaccination schedule) as well as of the follow-up phase for long-term safety and immunogenicity analysis (Month 9/12 data depending on the vaccination schedule).

Number of subjects at primary analysis (one month following last vaccination)

Number of subjects	Total	BivAS04	AS04016	AS1E016	AS2W016	AS1E03	AS1E06
Planned	540	90	90	90	90	90	90
Enrolled	540	90	92	89	90	89	90
Completed	536	90	90	88	90	88	90
Total Vaccinated cohort	540	90	92	89	90	89	90
ATP cohort for safety	527	87	88	86	88	88	90
ATP cohort for immunogenicity	514	86	85	84°	88	84	87°

ATP = According to protocol

° At six month following last vaccination analysis, one more subject from each the HPV-16/18/33/58 L1 VLP AS01E vaccine and HPV-16/18/33/58 L1 VLP AS01E (0, 6) vaccine groups was not included in the ATP cohort for immunogenicity.

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Diagnosis and criteria for inclusion:

- A woman between, and including, 18 and 25 years of age at the time of the first vaccination.
- Subjects who had had no more than 6 lifetime sexual partners prior to enrolment.
- Subjects of non-childbearing potential or, if of childbearing potential, abstinent or using adequate contraceptive precautions for 30 days prior to the first vaccination and agreeing to continue such precautions for two months after completion of the vaccination series.
- Without chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose or planned during the study period up to one month after last dose of vaccine (for corticosteroids, this meant prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids were allowed).
- Without previous vaccination against HPV or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period.
- Without previous administration of 3-deacylated monophosphoryl lipid A (MPL), *Quillaja saponaria* 21 (QS21), AS04, AS01E or AS02W adjuvants.
- Without any medically diagnosed or suspected immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- Without history of allergic disease, suspected allergy or reactions likely to be exacerbated by any component of the study vaccines (e.g. Aluminum, MPL, QS21, AS04, AS01E or AS02W).
- Without cancer or autoimmune disease under treatment.
- Without history of having had colposcopy or having planned a colposcopy to evaluate an abnormal cervical cytology (Pap smear) test.
- Without receiving immunoglobulins and/or blood product within 90 days preceding enrolment or planned administration during the study period up to one month after the last dose of vaccine. Enrolment was deferred until the subject was outside of specified window.
- Heavy bleeding (menstruation or other) or heavy vaginal discharge in which a cervical sample cannot be collected. Enrolment was deferred until condition was resolved according to investigators medical judgement.

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Study vaccine, dose, mode of administration, lot no.:

Vaccination schedule/site:

- 3-dose schedule: 3 doses of vaccine administered intramuscularly (IM) at Months 0, 1 and 6
- 2-dose schedule: 2 doses of vaccine administered IM at Months 0 and 6 or at Months 0 and 3.

Vaccine composition/dose/lot number:

Group	Vaccine	Formulation	Presentation	Volume	Number of doses	Lot number
AS04016	HPV-16/18/33/58 L1 VLP vaccine	20 µg HPV-16 L1 VLP, 20 µg HPV-18 L1 VLP, 20 µg HPV-33 L1 VLP, 20 µg HPV-58 L1 VLP	Suspension in 3mL glass vial	0.5mL	3	[redacted]
	AS04 adjuvant system	50 µg MPL 500 µg aluminum as $Al(OH)_3$				
AS1E016 **AS1E06** **AS1E03**	HPV-16/18/33/58 L1 VLP vaccine*	10 µg HPV-16 L1 VLP, 10 µg HPV-18 L1 VLP, 5 µg HPV-33 L1 VLP, 5 µg HPV-58 L1 VLP	Lyophilised pellet in 3mL monodose vial		2 or 3	[redacted]
	AS01E adjuvant system	25 µg MPL 25 µg QS21 12.5 µg Liposomes	Suspension in 3mL glass vial	0.5mL		[redacted]
AS2W016	HPV-16/18/33/58 L1 VLP vaccine*	10 µg HPV-16 L1 VLP, 10 µg HPV-18 L1 VLP, 5 µg HPV-33 L1 VLP, 5 µg HPV-58 L1 VLP	Lyophilised pellet in 3mL monodose vial		3	[redacted]
	AS02W adjuvant system	25 µg MPL 25 µg QS21 50 µl Emulsion	Pre-filled glass syringe	0.5mL		[redacted]

* Two vials of HPV-16/18/33/58 L1 VLP antigens were reconstituted with one vial of adjuvant.

Reference vaccine/Comparator, dose and mode of administration, lot no.:

Vaccination schedule /site:

According to a 3-dose schedule: 3 doses of vaccine administered IM at Months 0, 1 and 6.

Vaccine composition /dose /lot number:

Each dose of HPV-16/18 L1 VLP AS04 vaccine (BivAS04) contained 20 µg HPV-16 L1 VLP, 20 µg HPV-18 L1 VLP, 50 µg MPL, 500 µg aluminium [$Al(OH)_3$], 4.4 mg NaCl, 0.624 mg $NaH_2PO_4\,2H_2O$ and water for injection. BivAS04 is a turbid liquid suspension for injection, presented as a 0.5ml monodose vaccine in a 3ml monodose glass vial. Lot number: [redacted]

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Duration of treatment:

- Schedule 0, 3: approximately 9 months, i.e., 4 months (active phase) + 5 months follow-up for safety and immunogenicity for each subject
- Schedules 0, 6 and 0, 1, 6: approximately 12 months, i.e., 7 months (active phase) + 5 months follow-up for safety and immunogenicity for each subject.

Criteria for evaluation:

Co-primary endpoints:

Safety

- Occurrence, intensity and relationship to vaccination of any solicited local or general symptoms within 7 days (Days 0-6) after each vaccine dose.

Immunogenicity

- HPV-16 and HPV-18 seropositivity rates and geometric mean titres (GMTs) as assessed by ELISA at one month after the last dose of vaccine.

Secondary endpoints:

Safety

- Occurrence of serious adverse events (SAEs) up to one month after the last dose of vaccine.
- Occurrence, intensity and relationship to vaccination of any unsolicited symptom within 30 days (Days 0-29) after each vaccine dose.
- Occurrence of clinically relevant abnormalities in biochemical and haematological parameters assessed at Month 0, one month and six months after the last dose of vaccine.
- Occurrence of SAEs during the extended safety follow-up (up to six months after the last dose of vaccine).
- Occurrence of pregnancy and pregnancy outcomes, new onset chronic diseases (NOCDs, e.g., diabetes, new onset autoimmune disease [NOAD], asthma, allergies, etc.) or medically significant conditions (MSCs, i.e., adverse events (AEs) prompting emergency room or physician visits that are not related to common diseases, or SAEs that are not related to common diseases) throughout the study period, regardless of causal relationship to vaccination, and intensity were collected throughout the entire study period (Month 0 up to six months after the last dose of vaccine).

Immunogenicity

- HPV-16 and HPV-18 seropositivity rates and GMTs before the second dose of vaccine, at one month after the second dose of vaccine (for groups with the 3-dose schedule only), and at six months after the last dose of vaccine.
- HPV-33 and HPV-58 seropositivity rates and GMTs before the second dose of vaccine, at one month after the second dose of vaccine (for groups with the 3-dose schedule only) and at one month and six months after the last dose of vaccine.

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Exploratory endpoints:

- HPV-45, HPV-31 and HPV-52 seropositivity rates and GMTs before the second dose of vaccine, at one month after the second dose of vaccine (for 3-dose schedule groups) and at one month and six months after the last dose of vaccine.
- Cell mediated immune response related to HPV-16, 18, 31, 33, 45, 52 and 58 at Month 0, at one month after the second dose of vaccine (for 3-dose schedule groups), at one month and six months after the last dose of vaccine.

Statistical methods:

Analyses were performed as described in the protocol and the Report Analysis Plan (RAP) Amendment 1, dated 30 July 2008.

The statistician was blinded until the complete freezing of the database after study conclusion at one month following last vaccination (Month 7).

Safety analyses:

The primary analysis was based on the Total Vaccinated cohort. A second analysis based on the according to protocol (ATP) cohort for safety was performed to supplement the analysis on the Total Vaccinated cohort if at least 10% of vaccinated subjects were excluded from the ATP cohort.

- The percentage of subjects reporting and the percentage of doses followed by at least one local AE (solicited only and solicited and unsolicited combined), with at least one general AE (solicited only and solicited and unsolicited combined) and with any AE within the 7-day and 30-day follow-up period after each vaccination and overall were tabulated with their exact confidence interval (CI) by group according to the type of AE, their intensity and relationship to vaccination. The same tabulations were done for symptoms that resulted in a medically attended visit.
- The duration of solicited local and general symptoms during the solicited follow-up period was presented. The same analysis was done to present the duration of grade 3 solicited symptoms.
- The percentage of subjects reporting and the percentage of doses followed by at least one unsolicited AE (classified by the Medical Dictionary for Regulatory Activities [MedDRA], whenever available, and overall) within the 30-day follow-up period after any vaccination were tabulated with their exact 95% CI by group. The same tabulations were done for grade 3 unsolicited AEs, unsolicited AEs with causal relationship to vaccination and unsolicited AEs that resulted in a medically attended visit.
- The proportion of subjects with at least one report of a NOCD (analysed by GSK Assessment as well as by Investigator Assessment), including NOADs, classified by MedDRA, whenever available, and reported during the entire study period was tabulated with exact 95% CI.
- The proportion of subjects with at least one report of a MSC classified by MedDRA, whenever available, and reported up to 30 days after vaccination was tabulated with exact 95% CI. A similar table was produced for MSCs starting Day 30 after each dose until the end of the study.

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- The proportion of subjects with at least one report of a SAE, classified by MedDRA, whenever available, and reported during the entire study period was tabulated with exact 95% CI. SAEs and withdrawals due to AEs were described in detail.
- Haematology and biochemistry analysis included any abnormal values of creatinine, alanine amino-transferase (ALT), haematocrit, red blood cells (RBCs), platelets and white blood cells (WBCs, total and differential). The percentage of subjects outside the normal ranges as well as descriptive statistics for each relevant time point and for each laboratory safety parameter was calculated.

Immunogenicity analyses:

The primary analysis was based on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total Vaccinated cohort was performed to complement the ATP analysis if at least 10% of vaccinated subjects were excluded from the ATP cohort.

ATP cohort for immunogenicity at one month following last vaccination (primary analysis) is defined as ATP-1 and ATP cohort for immunogenicity at six months following last vaccination (secondary analysis) is defined as ATP-2 throughout this CSR. The primary immunogenicity endpoint results are presented for ATP-1. All other Immunogenicity endpoints are presented using ATP-2, since only 2 more subjects were excluded from ATP-2 compared to ATP-1.

For each vaccine group, at each time point for which a serological/CMI result was available:

- Seropositivity rates and GMTs with their 95% CIs for antibodies against HPV-16 and HPV-18 VLP L1 antigens as assessed by ELISA.
- Seropositivity rates and GMTs with their 95% CIs for antibodies against HPV-16, 18, 31, 33, 45, 52, 58 VLP L1 antigens as assessed by multiplex Luminex immuno assay (MLIA).
- Seropositivity rates and GMTs with their 95% CIs for HPV-16, 18, 31, 33, 45, 52, 58 pseudovirions (PSVs) as assessed by the pseudovirion-based neutralisation assay (PBNA).
- Frequency of HPV type-specific CD4 and CD8 T cells secreting at least 2 cytokines among CD40L, IL-2, TNF-α, and IFN-γ (all doubles) and secreting at least CD40L and/or IL-2 and/or TNF-α and/or IFN-γ (d-CD40L, d-IL2, d-TNF-α, d- IFN-γ) as measured by intracellular cytokine staining (ICS) at each time point for CMI was summarised for each vaccine group by the number of values (N), the number of missing values, and the mean, minimum, 1st quartile (Q1), median, 3rd quartile (Q3) and maximum, or the geometric mean (Gmean) with 95% CI. Values of 0 were given an arbitrary value of 1 for the purpose of Gmean calculation.
- For each ICS assay and for each HPV type at each time point for CMI sampling, the number and percentage of subjects above a defined threshold was calculated (with the threshold defined as the 95th percentile of the frequency of CD4 or CD8 T cells [all doubles] stimulated by a HPV type-specific antigen at Month 0 [i.e., ≥250/200 CD4/CD8 T cells/10^6 CD4/CD8 T cells] or defined as frequencies equal to or above 500 CD4 T cells/10^6 CD4 T cells) at each time point.
- Frequency of HPV type-specific B cells at each time point for CMI sampling was summarised for each vaccine group by the number of values (N), the number of missing values, and the mean, minimum, Q1, median, Q3 and maximum, or the Gmean with 95%CI. Values of 0 were given an arbitrary value of 1 for the purpose of Gmean calculation.

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- For each HPV type-specific antigen, the number and percentage of subjects with a frequency of HPV type-specific B cells above 0 was calculated at each time point.

T cell and B cell analyses were performed on two different sub-cohorts:

- Subjects who were DNA negative and seronegative to the corresponding HPV type at baseline (i.e., for response against HPV-16, DNA- and S- subjects for HPV-16). For B cell analysis, subjects had to be in addition B cell negative for the corresponding HPV type.
- Subjects who were DNA negative and seronegative to all related HPV types at baseline (i.e., for response against HPV-16, DNA- and S- subjects for HPV-16/31/33/52/58 and for response against HPV-18, DNA- and S- subjects for HPV-18/45).

Between groups assessment of antibody responses to HPV vaccine types was done on a sub-cohort of subjects in ATP cohort for immunogenicity who were initially seronegative and DNA negative (by polymerase chain reaction [PCR]) at baseline for the corresponding HPV type and the corresponding assay.

For the primary endpoint (HPV-16 and HPV-18 L1 VLP antibody responses by ELISA), the 6 different vaccine groups were compared in terms of HPV-16 and HPV-18 L1 VLP antibody GMTs at one month after the last vaccination (Month 7 or Month 4 depending on the schedule) using a One-way analysis of variance (ANOVA) F-test. If a statistical difference was found (p-value ≤ 0.025), pair-wise comparisons were made using Tukey's multiple comparison adjustment. The same analysis was done by using HPV-16/18 GMTs as measured by MLIA.

For the secondary endpoint related to HPV-33 and HPV-58 L1 VLP antibody response (by MLIA), the 5 different vaccine groups containing HPV-33 and HPV-58 (excluding the control vaccine group) were compared in terms of HPV-33 and HPV-58 L1 VLP antibody GMTs at one month after the last vaccination (Month 7 or Month 4 depending on the schedule) using a One-way ANOVA F-test as measured by MLIA. If a statistical difference was found (p-value ≤ 0.025), pair-wise comparisons were made using Tukey's multiple comparison adjustment.

For PBNA, no between groups comparison was performed.

For HPV-16/18/33/58 L1 VLP antibody responses, the same analysis was done at 6 months after the last dose (Month 12 or Month 9 depending on the schedule) by considering an alpha level of 0.05.

Summary:

Demography:

The demographic characteristics of subjects in the Total vaccinated cohort were comparable between all vaccine groups with respect to mean age, height and weight. Overall, the mean age was 21.1 years (range: 18-25 years) and the majority of participating females were of Caucasian heritage (96.3%).

In the ATP-1, 70.2% of subjects were seronegative for all vaccine HPV types analysed, whereas 3.5% of subjects were seropositive for all HPV types present in the HPV-16/18/33/58 vaccine formulations, with 18.1%, 15%, 13.3%, and 8.3% of subjects who were seropositive (by MLIA) at baseline for anti-HPV-58, anti-HPV-16, anti-HPV-33, and anti-HPV-18 antibodies, respectively. At baseline, 91.9% of subjects were DNA negative for all vaccine HPV types, and no subjects were HPV DNA positive for all vaccine HPV types, with 5.9% of subjects who were DNA positive HPV-16, and ≤ 1.4 % of subjects who were DNA positive for any other vaccine HPV type.

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Immunogenicity:

Immunogenicity analysis was performed on the ATP cohort for immunogenicity.

Anti-HPV-16 and anti-HPV-18 antibody responses at one month following last vaccination as measured by ELISA (primary endpoint in ATP-1):

At one month following last vaccination, all subjects were seropositive for anti-HPV-16 antibodies in all vaccine groups. GMTs for anti-HPV-16 antibodies gradually increased over time to high values (GMT range in initially seronegative subjects: 6651-27437.2 ELU/mL) at one month following last vaccination in all vaccine groups.

Comparison of the anti-HPV-16 antibody response at one month following last vaccination between different vaccine formulations in initially seronegative and DNA negative subjects revealed that:

- The anti-HPV-16 antibody response was significantly lower when HPV-33 and HPV-58 antigens were added to the HPV-16/18 L1 VLP AS04 vaccine (GMTs in initially seronegative subjects: 6651 vs. 11092.6 ELU/mL).
- The anti-HPV-16 antibody response was significantly higher in the tetravalent vaccine groups containing the new adjuvants (AS02W and AS01E) and administered according to a 3-dose schedule compared to the control vaccine (GMTs in initially seronegative subjects: 18150.3 and 27437.2 ELU/mL, respectively, vs. 11092.6 ELU/mL).
- The anti-HPV-16 antibody response was also significantly higher when new adjuvants were added to the HPV-16/18/33/58 antigens as compared to AS04, even when administered in a 2-dose schedule. Highest response was elicited by the HPV-16/18/33/58 L1 VLP AS01E vaccine when administered in a 3-dose schedule.
- The anti-HPV-16 antibody response was significantly higher when 3 doses of the tetravalent vaccine formulation (adjuvanted with AS01E) were administered compared to that induced by 2 doses of the same vaccine formulation (GMTs in initially seronegative subjects: 27437.2 vs. 11923.8 (0, 6) or 11415.8 (0, 3) ELU/mL, whereas there was no significant difference between the different 2-dose schedules.

At one month following last vaccination, all subjects were seropositive for HPV-18 antibodies in all vaccine groups. GMTs for anti-HPV-18 antibodies gradually increased over time to high values (GMT range in initially seronegative subjects: 1944.2-4534.9 ELU/mL) at one month following last vaccination in all vaccine groups.

Comparison of the anti-HPV-18 antibody responses at one month following last vaccination between different vaccine formulations in initially seronegative and DNA negative subjects revealed that:

- The anti-HPV-18 antibody response was lower when HPV-33 and HPV-58 antigens were added to the HPV-16/18 L1 VLP AS04 vaccine (GMTs in initially seronegative subjects: 2956 vs. 4534.9 ELU/mL), although this difference was not significant.
- The anti-HPV-18 antibody response was also lower in the tetravalent vaccine groups containing the new adjuvants, independent from the dose schedule, compared to the control vaccine (GMTs in initially seronegative subjects: 1944.2-3077.2 ELU/mL for the new adjuvanted groups vs. 4534.9 ELU/mL for the control vaccine group), although this difference was not significant with the HPV-16/18/33/58 L1 VLP AS01E vaccine group administered according to the 3-dose schedule.

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- There was no significant difference in anti-HPV-18 antibody response induced by the HPV-16/18/33/58 L1 VLP AS04 vaccine and the tetravalent vaccine formulations containing the new adjuvants when administered in a 3-dose schedule.
- The anti-HPV-18 antibody response was significantly higher when 3 doses of the tetravalent vaccine formulation (adjuvanted with AS01E) were administered compared to that induced by 2 doses of the same vaccine formulation (GMTs in initially seronegative subjects: 3077.2 vs. 1944.2 (0, 6) or 1972 (0, 3) ELU/mL, respectively), whereas there was no significant difference between the different 2-dose schedules.

Anti-HPV-16 and anti-HPV-18 antibody responses (by ELISA) at one month after the last vaccination in subjects who were seronegative for the corresponding HPV type at baseline

Anti-HPV-16 antibody response (ELISA) in ATP-1

Group	Timing	N	Seropositivity rate (≥ 8 ELU/mL)				GMTs		
			n	%	95% CI		value	95%CI	
					LL	UL		LL	UL
BivAS04	PRE	63	0	0.0	0.0	5.7	4.0	4.0	4.0
	PI(M1)	63	63	100	94.3	100	368.5	293.9	461.9
	PII(M2)	63	63	100	94.3	100	2960.2	2502.4	3501.8
	PIII(M7)	63	63	100	94.3	100	11092.6	8812.8	13962.4
AS04016	PRE	66	0	0.0	0.0	5.4	4.0	4.0	4.0
	PI(M1)	66	66	100	94.6	100	330.1	273.6	398.1
	PII(M2)	65	65	100	94.5	100	1858.1	1592.4	2168.2
	PIII(M7)	64	64	100	94.4	100	6651.0	5390.7	8205.9
AS1E016	PRE	68	0	0.0	0.0	5.3	4.0	4.0	4.0
	PI(M1)	67	67	100	94.6	100	634.8	532.4	757.0
	PII(M2)	68	68	100	94.7	100	6195.3	5416.3	7086.3
	PIII(M7)	68	68	100	94.7	100	27437.2	23375.8	32204.2
AS2W016	PRE	68	0	0.0	0.0	5.3	4.0	4.0	4.0
	PI(M1)	68	68	100	94.7	100	578.6	482.9	693.2
	PII(M2)	68	68	100	94.7	100	5763.0	4874.6	6813.2
	PIII(M7)	68	68	100	94.7	100	18150.3	15325.7	21495.4
AS1E13	PRE	64	0	0.0	0.0	5.6	4.0	4.0	4.0
	PI(M3)	64	64	100	94.4	100	294.8	238.0	365.1
	PII(M4)	63	63	100	94.3	100	11415.8	10170.8	12813.2
AS1E16	PRE	70	0	0.0	0.0	5.1	4.0	4.0	4.0
	PI(M6)	70	70	100	94.9	100	126.1	101.4	156.7
	PII(M7)	70	70	100	94.9	100	11923.8	10267.5	13847.4

N = number of seronegative subjects with pre-vaccination results available
n/% = number/percentage of seronegative subjects with concentration within the specified range
GMT = geometric mean antibody concentration calculated on all seronegative subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

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Anti-HPV-18 antibody response (ELISA) in ATP-1

Group	Timing	N	Seropositivity rate (≥ 8 ELU/mL)				GMTs		
			n	%	95% CI		value	95%CI	
					LL	UL		LL	UL
BivAS04	PRE	74	0	0.0	0.0	4.9	3.5	3.5	3.5
	PI(M1)	74	74	100	95.1	100	222.1	181.4	272.0
	PII(M2)	74	74	100	95.1	100	2277.0	1901.1	2727.3
	PIII(M7)	74	74	100	95.1	100	4534.9	3721.5	5526.0
AS04016	PRE	75	0	0.0	0.0	4.8	3.5	3.5	3.5
	PI(M1)	75	75	100	95.2	100	187.2	150.9	232.1
	PII(M2)	74	74	100	95.1	100	1740.1	1473.8	2054.5
	PIII(M7)	73	73	100	95.1	100	2956.0	2420.9	3609.4
AS1E016	PRE	73	0	0.0	0.0	4.9	3.5	3.5	3.5
	PI(M1)	73	73	100	95.1	100	231.0	184.7	288.9
	PII(M2)	73	73	100	95.1	100	1824.1	1505.4	2210.2
	PIII(M7)	73	73	100	95.1	100	3077.2	2532.1	3739.6
AS2W016	PRE	78	0	0.0	0.0	4.6	3.5	3.5	3.5
	PI(M1)	78	78	100	95.4	100	164.2	134.4	200.6
	PII(M2)	78	78	100	95.4	100	1790.8	1475.7	2173.2
	PIII(M7)	78	78	100	95.4	100	2204.8	1891.3	2570.2
AS1E13	PRE	74	0	0.0	0.0	4.9	3.5	3.5	3.5
	PI(M3)	74	74	100	95.1	100	191.6	148.2	247.7
	PII(M4)	73	73	100	95.1	100	1972.0	1658.6	2344.8
AS1E16	PRE	74	0	0.0	0.0	4.9	3.5	3.5	3.5
	PI(M6)	74	73	98.6	92.7	100	86.9	65.3	115.6
	PII(M7)	74	74	100	95.1	100	1944.2	1637.7	2307.9

N = number of seronegative subjects with pre-vaccination results available
n/% = number/percentage of seronegative subjects with concentration within the specified range
GMT = geometric mean antibody concentration calculated on all seronegative subjects
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

At six months following last vaccination, all subjects remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies in all vaccine groups, with decreasing but sustained high levels of GMTs (range in initially seronegative subjects: 2675.4-14603.6 ELU/mL and 377.7-1583.8 ELU/mL).

Similar results were obtained when the anti-HPV-16 and anti-HPV-18 antibody responses were measured by MLIA or by PBNA.

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Anti-HPV-33 and anti-HPV-58 antibody response at one month following last vaccination as measured by MLIA (secondary endpoint):

At one month following last vaccination, all subjects were seropositive for anti-HPV-33 antibodies in all vaccine groups, including the control vaccine (HPV-16/18 L1 VLP AS04) group. In all tetravalent vaccine groups, GMTs for anti-HPV-33 antibodies gradually increased over time to high levels at one month following last vaccination in the 3-dose schedule groups (GMT range in initially seronegative subjects: 7083.4-21632.1 LU/mL) as well as in the 2-dose schedule groups (GMT range in initially seronegative subjects: 11701.1-15604.2). GMTs for anti-HPV-33 antibodies were highest in the HPV-16/18/33/58 L1 VLP AS01E vaccine group and lowest in the HPV-16/18/33/58 L1 VLP AS04 vaccine group. In the control vaccine group, GMTs for anti-HPV-33 antibodies were 145.4 LU/mL at one month following last vaccination.

At one month following last vaccination, all subjects were seropositive for anti-HPV-58 antibodies in all vaccine groups, including the control vaccine (HPV-16/18 L1 VLP AS04) group. In all tetravalent vaccine groups, GMTs for anti-HPV-58 antibodies gradually increased over time to high levels at one month following last vaccination in the 3-dose schedule groups (GMT range in initially seronegative subjects: 5449-11080.9 LU/mL) as well as in the 2-dose schedule groups (GMT range in initially seronegative subjects: 5192.3-7035.1 LU/mL). GMTs for anti-HPV-58 antibodies were highest in the HPV-16/18/33/58 L1 VLP AS01E vaccine group and lowest in the HPV-16/18/33/58 L1 VLP AS04 vaccine group. In the control vaccine group, GMTs for anti-HPV-58 antibodies 112.3 LU/mL at one month following last vaccination.

At six months following last vaccination, all subjects remained seropositive for anti-HPV-33 and anti-HPV-58 antibodies in all tetravalent vaccine groups, with decreasing but sustained high levels of GMTs (range in initially seronegative subjects: 2766.2-9937.2 LU/mL and 1207.5-4441.4 LU/mL, respectively). At this time point, the HPV-16/18/33/58 L1 VLP AS01E vaccine administered according to the Months 0, 6 2-dose schedule induced a significantly higher anti-HPV-33 antibody response than the HPV-16/18/33/58 L1 VLP AS01E vaccine administered according to the Months 0, 3 2-dose schedule as measured in initially seronegative subjects (GMTs: 4697.4 vs. 2979.4 LU/mL).

Similar results were obtained when the anti-HPV-33 and anti-HPV-58 antibody responses were measured by PBNA.

Cross immune response to HPV-31, HPV-45 and HPV-52 antigens (exploratory endpoint):

Cross-reactive antibody responses to HPV-31, HPV-45 and HPV-52 antigens were rather weak in all tetravalent vaccine groups receiving 2 or 3 doses as well as in the control vaccine group (GMT range in initially seronegative subjects: 260.9-1083.1, 194.2-357.3 and 151-612.5 LU/mL at one month following last vaccination and 72.8-408.5, 53.8-136.3 and 27.1-140.5 LU/mL at six months following last vaccination, respectively).

B cell response to HPV-16, HPV-18, HPV-33 and HPV-58 antigens (exploratory endpoint):

At one month following last vaccination, ≥ 84.2% of subjects had a specific B cell response to HPV-16, HPV-18, HPV-33 and HPV-58 antigens when considering all vaccine groups. There was a substantial increase from baseline in HPV-16 and HPV-18 specific frequencies of memory B cells in all vaccine groups and also in HPV-33 and HPV-58 specific frequencies of memory B cells in all tetravalent vaccine groups at one month following last vaccination.

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At one month following last vaccination, memory B cell responses to HPV-16 and HPV-18 were lower when HPV-33 and HPV-58 were added to the HPV-16/18 AS04 (control) vaccine. The control vaccine showed a low memory B cell response to HPV-33 and HPV-58 compared to the tetravalent AS04-adjuvanted vaccine. The tetravalent HPV-16/18/33/58 L1 VLP vaccine adjuvanted with AS01E, independent of the dose schedule, induced a higher HPV type-specific B cell response to all vaccine HPV antigens than the tetravalent vaccine adjuvanted with AS04.*T cell response to HPV-16, HPV-18, HPV-33 and HPV-58 antigens (exploratory endpoint):*

At one month following last vaccination, > 80% of subjects had a specific CD4 T cell response to HPV-16, HPV-18, HPV-33 and HPV-58 (≥ 250 HPV-specific CD4 T cells/10^6 CD4 T cells secreting at least 2 different cytokines ["all doubles"]) in all vaccine groups.

HPV type-specific CD4 T cell frequencies were considerably increased from baseline at one month after the second vaccination in the 2-dose schedule groups as well as in the 3-dose schedule groups, and were not boosted by the third vaccination.

At one month following last vaccination, CD4 T cell responses to HPV-16 and HPV-18 were lower when HPV-33 and HPV-58 were added to the HPV-16/18 AS04 (control) vaccine. Frequencies of CD4 T cells specific to HPV-33 and HPV-58 were similar between the control vaccine group and the tetravalent AS04-adjuvanted vaccine group. The tetravalent HPV-16/18/33/58 L1 VLP vaccine adjuvanted with AS01E, independent of the dose schedule, induced a higher HPV type-specific CD4 T cell response to all vaccine HPV antigens than the tetravalent vaccine adjuvanted with AS04.

No specific CD8 T cell response to any of the vaccine HPV types was detected.

Safety/reactogenicity:

The safety analysis was performed on the Total Vaccinated cohort.

Solicited adverse events (primary endpoint):

Solicited local symptoms were reported following 91.9% of doses in the control vaccine group compared to 94.5% of doses in the HPV-16/18/33/58 L1 VLP AS04 vaccine group and 93.7% to 98.3% of doses in tetravalent vaccine groups containing new adjuvants. Grade 3 solicited local symptoms were reported following 5.2% of doses in the control vaccine group compared to 6.9% of doses in the HPV-16/18/33/58 L1 VLP AS04 vaccine group and 8.7% to 11.1% of doses in tetravalent vaccine groups containing new adjuvants. The most frequently reported solicited local symptom was pain at the injection site, following 91.1% in the control vaccine group and following 93.7% to 98.3% of doses across tetravalent vaccine groups. Redness was reported with higher incidence in the control vaccine, HPV-16/18/33/58 L1 VLP AS04 vaccine and HPV-16/18/33/58 L1 VLP AS01E vaccine groups compared to the HPV-16/18/33/58 L1 VLP AS02W vaccine and HPV-16/18/33/58 L1 VLP AS01E (0, 3) vaccine groups (23.3%-24.1% vs. 10.2%-13%). Swelling was reported following 19.2% of doses in the control vaccine group and following 15.3% to 22.6% of doses across tetravalent vaccine groups. The most frequently reported grade 3 solicited local symptom was pain at the injection site, following 4.1% in the control vaccine group and 4.9% to 10% of doses across tetravalent vaccine groups. The reporting of grade 3 redness and swelling was lower and similar between vaccine groups, i.e. following 0% to 2.6% and 0.6% to 3.4% of doses, respectively. Overall, the mean duration of solicited local symptoms per dose was short (range: 2.2 to 3.3 days for any solicited local symptom) and similar between vaccine groups.

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Solicited general symptoms were reported following 55.6%% of doses in the control vaccine group compared to 59.9% of doses in the HPV-16/18/33/58 L1 VLP AS04 vaccine group, 60.4% of doses in the HPV-16/18/33/58 L1 VLP AS02W vaccine group and 68.3% to 76.1% of doses in the HPV-16/18/33/58 L1 VLP AS01E vaccine groups. Grade 3 solicited general symptoms were reported following 1.9% of doses in the control vaccine group compared to 3.3% of doses in the HPV-16/18/33/58 L1 VLP AS04 vaccine group, 6.3% of doses in the HPV-16/18/33/58 L1 VLP AS02W vaccine group and 7.2% to 12.1% of doses in the HPV-16/18/33/58 L1 VLP AS01E vaccine groups. The most commonly reported solicited general symptoms (> 20% of doses in any vaccine group) in decreasing order were fatigue, headache, myalgia and gastrointestinal disorders. All solicited general symptoms, except rash and urticaria, occurred with higher frequency in the AS01E-adjuvanted vaccine groups than in the vaccine groups containing the AS04 or AS02W adjuvant. Overall, few grade 3 solicited general symptoms were reported (< 5% of doses), except for fatigue (5.7% of doses) and headache (6% of doses) in the HPV-16/18/33/58 L1 VLP AS01E vaccine group. In all vaccine groups, the majority of solicited general symtoms was considered related to vaccination by the investigator. Overall, the mean duration of (grade 3) solicited general symptoms per dose was short (range: 1.0 to 2.7 days) and comparable between vaccine groups, except for rash and urticaria who lasted 4.3 and 3.8 days, respectively, in the HPV-16/18/33/58 L1 VLP AS01E (0, 6) vaccine group.

In conclusion, there was a trend of increased reactogenicity profile during the 7-day post-vaccination period when adding HPV-33 and HPV-58 antigens to the bivalent HPV vaccine (control), which was even more pronounced with the tetravalent vaccine formulations containing the new adjuvants (AS02W and AS01E).

Overall incidence and nature of solicited symptoms reported during the 7-day (Days 0-6) post-vaccination period

		General symptoms					Local symptoms				
					95% CI					95% CI	
Overall /dose	Group	N	n	%	LL	UL	N	n	%	LL	UL
All	BivAS04	270	150	55.6	49.4	61.6	270	248	91.9	87.9	94.8
	AS04016	274	164	59.9	53.8	65.7	274	259	94.5	91.1	96.9
	AS1E016	265	181	68.3	62.3	73.9	265	254	95.8	92.7	97.9
	AS2W016	270	163	60.4	54.3	66.2	270	253	93.7	90.1	96.3
	AS1E03	176	132	75.0	67.9	81.2	177	171	96.6	92.8	98.7
	AS1E06	180	137	76.1	69.2	82.1	180	177	98.3	95.2	99.7
Grade 3	BivAS04	270	5	1.9	0.6	4.3	270	14	5.2	2.9	8.5
	AS04016	274	9	3.3	1.5	6.1	274	19	6.9	4.2	10.6
	AS1E016	265	32	12.1	8.4	16.6	265	23	8.7	5.6	12.7
	AS2W016	270	17	6.3	3.7	9.9	270	26	9.6	6.4	13.8
	AS1E03	176	17	9.7	5.7	15.0	177	19	10.7	6.6	16.3
	AS1E06	180	13	7.2	3.9	12.0	180	20	11.1	6.9	16.6

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Unsolcited adverse events:
Overall, unsolicited symptoms were reported following 28.5% of doses in the control vaccine group and following 26.8% to 41.9% of doses across tetravalent vaccine groups during the 30-day post-vaccination period. Unsolicited symptoms were more frequently reported in the HPV-16/18/33/58 L1 VLP AS02W and AS01E vaccine groups (36% to 41.9%) than in the AS04-adjuvanted vaccine groups (26.8% to 28.5%). The most commonly reported unsolicited symptom was injection site pruritus, reported following 5.2% of doses in the HPV-16/18/33/58 L1 VLP AS02W vaccine group. No other unsolicited symptoms were reported following more than 5% of doses in any vaccine group. Grade 3 unsolicited symptoms were reported with a higher frequency in the HPV-16/18/33/58 L1 VLP AS01E (0, 6) vaccine group (following 11.1% of doses) than in the other vaccine groups (following 4% to 6.4% of doses). No grade 3 unsolicited symptoms were reported following more than 3 doses in any vaccine group, except gastroenteritis that was reported following 4 doses in the HPV-16/18/33/58 L1 VLP AS04 vaccine group. Unsolicited symptoms assessed by the investigator as possibly related to vaccination were reported with higher frequency following vaccine doses containing AS01E and AS02W adjuvants than when receiving AS04-adjuvanted vaccine doses, i.e. following 13.5% to 19.6% vs. 8.1% to 8.3% of doses, respectively. Administration site reactions were reported following 3.3% to 10.4% of doses across vaccine groups. In the 3-dose schedule group, administration site conditions were more frequently reported in the vaccine groups receiving the AS01E (9.8%) and AS02W (10.4%) adjuvants than in the control vaccine group (3.3%) and HPV-16/18/33/58 L1 VLP AS04 vaccine group (4%). All, except one of these events were considered related to vaccination. No other unsolicited symptoms with causal relationship to vaccination were reported following > 2% of doses in any vaccine group.

Serious adverse events:
Overall, for 9 subjects 9 SAEs were reported during the active phase of the study, i.e., from study start until one month after last vaccination. In addition, one other subject was reported with the SAE of recurrent tonsillitis at an unspecified date around first vaccination. During the safety follow-up phase, i.e., from one month following the last vaccination onwards until the end of the study (6 months following last vaccination), 3 more subjects were reported with 5 SAEs. The incidence rate of SAEs reported during the entire study period (from first vaccination until 6 months following last vaccination) was similar between vaccine groups, with at most 3 subjects in any vaccine group. None of these SAEs were fatal or were considered related to vaccination by the investigator.

Withdrawals due to adverse events:
No subjects were withdrawn from the study due to a (S)AE.

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Adverse events of specific interest:
Overall, for 12 subjects 12 NOCDs were reported during the active phase of the study (GSK assessment). During the safety follow-up phase, for 2 more subjects, a NOCD was assessed by GSK. The incidence rate of NOCDs reported during the study entire period was similar between vaccine groups (1.1% to 5.6% of subjects). The most commonly reported NOCD was allergy to arthropod bite and urticaria, reported in 7 and 2 subjects, respectively. All other NOCDs (autoimmune thyroiditis, colitis ulcerative, allergy to arthropod sting, hypersensitivity and seasonal allergy) were reported in at most 1 subject in any vaccine group. None of these NOCDs were SAEs, but the 2 events of urticaria were considered related to vaccination by the investigator. During the entire study period, one subject in each the control vaccine and HPV-16/18/33/58 L1 VLP AS02W vaccine groups reported a NOCD considered by GSK as an NOAD, colitis ulcerosa and autoimmune thyroiditis, respectively.
Overall, for 94 subjects 116 MSCs were reported during the active phase of the study. During the safety follow-up phase, for 9 more subjects, a MSC was reported. MSCs were reported for 10.1% to 28.9% of subjects across all vaccine groups during the study entire period, with the highest incidence rate in the HPV-16/18/33/58 L1 VLP AS02W vaccine group and the lowest incidence rate in the HPV-16/18/33/58 L1 VLP AS01E (0, 3) vaccine group. Individual MSCs were reported in at most 3 subjects in any vaccine group, except cystitis was reported in 5 (5.6%) subjects in the HPV-16/18/33/58 L1 VLP AS02W vaccine group.

Pregnancies:
Two subjects became pregnant during the active phase of the study, one in the HPV-16/18/33/58 L1 VLP AS01E vaccine group and another in the HPV-16/18/33/58 L1 VLP AS01E (0, 6) vaccine group. The outcomes of both pregnancies were elective abortion. During the long-term follow-up period of the study, 2 more subjects were reported to be pregnant, one in the control vaccine group and another in the HPV-16/18/33/58 L1 VLP AS01E vaccine. The first gave birth to a healthy normal infant, while for the latter subject's pregnancy no follow-up information was available at the time of reporting.

Laboratory safety parameters:
In all vaccine groups, no clinically relevant differences from baseline were observed in haematological and biochemical analyses at one and six months following last vaccination.

Conclusions:
This adjuvant-selection study assessed the safety and immunogenicity of the first administration in humans of the tetravalent HPV-16/18/33/58 L1 VLP vaccine combined with 3 different adjuvants and administered in 3 different schedules in healthy women aged between 18 and 25 years compared to the bivalent HPV-16/18 L1 AS04 vaccine.

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of finished product:** GlaxoSmithKline Biologicals' human papillomavirus (HPV) next generation vaccine **Name of active substance:** HPV-16 L1 VLP protein HPV-18 L1 VLP protein HPV-33 L1 VLP protein HPV-58 L1 VLP protein	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- The immune response at one month following last vaccination to the HPV-16/18/33/58 antigens was high in all different vaccine groups, both in terms of GMTs and seropositivity rates (100% in all subjects).
- Comparison of antibody responses between vaccine formulations at one month following the last vaccination in initially seronegative and DNA negative subjects revealed that:
  - The tetravalent HPV-16/18/33/58 L1 VLP vaccine containing the AS04 adjuvant induced a significantly lower anti-HPV-16 antibody response than the control vaccine (HPV-16/18 L1 VLP AS04). In contrast, the tetravalent HPV-16/18/33/58 L1 VLP vaccine adjuvanted with new adjuvants (AS02W and AS01E) and administered according to a 3-dose schedule induced significantly higher anti-HPV-16 antibody responses than the control vaccine and the HPV-16/18/33/58 L1 VLP AS04 vaccine. The anti-HPV-16 antibody response was significantly higher in the HPV-16/18/33/58 L1 VLP AS01E vaccine group compared to the HPV-16/18/33/58 L1 VLP AS02W vaccine group, with a significantly higher anti-HPV-16 antibody response when administered according to a 3-dose schedule compared to a 2-dose schedule.
  - The tetravalent HPV-16/18/33/58 L1 VLP vaccine containing the AS04 adjuvant induced a lower anti-HPV-18 antibody response than the control vaccine (HPV-16/18 L1 VLP AS04), but this difference was not significant. Anti-HPV-18 responses were also lower in the tetravalent vaccine groups with new adjuvants compared to the control vaccine group (with significant difference with AS02W adjuvant). No significant differences were observed in anti-HPV-18 antibody responses between the different tetravalent vaccine formulations when administered in 3 doses. The anti-HPV-18 antibody response was significantly higher when the HPV-16/18/33/58 L1 VLP AS01E vaccine was administered in 3 doses compared to 2 doses.
- In all other tested assays, the tetravalent HPV-16/18/33/58 L1 VLP vaccine adjuvanted with AS01E and administered according to a 3-dose schedule of 0, 1, and 6 months induced the highest HPV type-specific antibody responses to all vaccine HPV antigens and also to cross-reactive HPV-31, HPV-45 and HPV-52 antigens when compared with the other 3-dose schedule tetravalent vaccine groups. When the HPV-16/18/33/58 L1 VLP AS01E vaccine was administered in 2 doses, the HPV type-specific antibody response to all HPV antigens tested was lower and less persistent than when receiving 3 doses, and was independent of the dose schedule (0, 3 months and 0, 6 months).
- Generally, the reactogenicity and safety profile of the different vaccine formulations of the HPV-16/18/33/58 L1 VLP vaccine was satisfactory. However, there was a consistent trend for higher reactogenicity when HPV-33 and HPV-58 antigens were added to the HPV-16/18 L1 VLP AS04 vaccine, which was more pronounced with tetravalent vaccine formulations containing new adjuvants (AS02W and especially AS01E).

In conclusion, the tetravalent vaccine formulation adjuvanted with AS01E and administered in 3 doses induced the highest immune response to all HPV-16/18/33/58 antigens, although it was also more reactogenic than the other vaccine formulations, especially when considering solicited general symptoms.

Date of report: 29 January 2010