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Human papillomavirus 16/18 AS04-adjuvanted cervical cancer vaccine: immunogenicity and safety in 15-25 years old healthy Korean women

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Objective: The study assessed the immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Korean women aged 15-25 years.

Methods: Phase IIIB, double-blind, randomised (2:1), multi-centre trial was conducted in Korea from June 2007 to March 2008. The study enrolled 225 women in the HPV (N=149) and placebo (N=76) groups who received three doses of HPV-16/18 AS04-adjuvanted vaccine or placebo (aluminium hydroxide) administered intramuscularly at 0, 1, and 6 months and were followed until one month post-dose 3. Serum samples were collected pre-vaccination and one month post-dose 3. Safety and reactogenicity data were collected throughout.

Results: In this trial, 208 women completed the study (141 in HPV group; 67 in placebo group). At month 7, all initially seronegative women had seroconverted for HPV-16 and HPV-18 antibodies with anti-HPV-16 and anti-HPV-18 geometric mean titres of 9,351.4 El.U/mL (95% CI, 8,145.5 to 10,735.8) and 4204.1 El.U/mL (95% CI, 3,626.5 to 4,873.6), respectively. Initially seropositive women showed similar increase in geometric mean titre levels. Compliance to the three dose vaccination course was 95.3% in HPV and 89.5% in placebo group. Solicited local (pain) and general (fatigue, myalgia or headache) symptoms were commonly reported in both groups. Three serious adverse events were reported (two in HPV group; one in placebo group), all unrelated to vaccination by the investigator; all recovered.

Conclusion: The HPV-16/18 AS04-adjuvanted vaccine was highly immunogenic with a clinically acceptable safety profile in Korean women. This study was in line with previous global studies in Europe, North America, and Brazil. (ClinicalTrials.gov number, NCT 00485732.)

Keywords: AS04-adjuvanted, Cervical cancer, Geometric mean titres, Human papillomavirus-16/18, Immunogenicity, Seroconversion

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INTRODUCTION

Cervical cancer is the second most common form of cancer in women worldwide, with approximately 555,100 new cases and 309,800 deaths reported in 2007; 83% of these cervical cancer deaths occur in developing countries [1]. The pattern of cervical cancer incidence and mortality in Korea is similar to that seen in a developing country setting [2].

In Korea, cervical cancer is the fifth most common malignant cancer reported with over 3,000 women developing this disease annually [3], and accounting for 9.8% of new cancer cases in Korean women [4]. The age-standardised rate (ASR) for cervical cancer has shown a decline from 19 per 100,000 women in 1993-1995 to 15 per 100,000 women in 1999-2002 in Korea [2]. According to Cancer Incidence in Five Continents (Volume IX), the ASR for cervical cancer in Korea has shown to be intermediate at 15.4 per 100,000 women [5].

Amongst the various risk factors associated with cervical cancer [6], persistent infection with oncogenic human papillomavirus (HPV) types is established as an essential precursor to the development of cervical cancer [7,8]. Of the 15 oncogenic HPV types identified, HPV-16 and HPV-18 together account for approximately 70% of all invasive cervical cancer (ICC) cases worldwide, with HPV-45, -33, and -31 accounting for additional approximately 10% of reported cases [9]. In Korea, HPV-16, -18, -58, -33, and -52 accounts for 80.8% of all ICC cases, while 65.1% of ICC are caused by HPV-16 and -18 alone. The prevalence of HPV-58, -33, and -52 is high in high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer in Korean women when compared to many other countries [10].

The World Health Organisation (WHO) has recognised cervical cancer and other HPV-related diseases as a global public health problem and recommends the inclusion of routine HPV vaccination in national immunisation programmes worldwide [11]. The HPV-16/18 AS04-adjuvanted cervical cancer vaccine (*Cervarix*®, GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium) has been developed and licensed in more than 100 countries worldwide, including US, Europe, Japan, and Korea. In addition, a pre-qualification has been awarded to *Cervarix*® by the WHO to ensure access of the vaccine and help combat cervical cancer in developing countries [12]. The vaccine has been shown to be immunogenic and having a clinically acceptable safety profile in global clinical studies [13-18], and high efficacy against persistent HPV-16/18 infection and CIN2+ up to 6.4 years after vaccination [13,19].

Over 58,000 girls and women are currently enrolled in/ have participated in clinical trials for the HPV-16/18 AS04-adjuvanted cervical cancer vaccine. The vaccine is already in use as part of routine immunisation programmes in countries such as the Netherlands and the UK to protect women against cervical cancer [20,21].

This phase IIIB study was conducted in healthy Korean women aged 15-25 years to evaluate the immunogenicity, safety and reactogenicity of the vaccine.

MATERIALS AND METHODS

1. Study design and participants

Healthy Korean women aged 15-25 years at the time of first vaccination were recruited for this phase IIIB, double-blind, placebo-controlled, multi-centre trial conducted from June 2007 to March 2008 in six Korean centres (Study ID:107291). Women were randomised (2:1, vaccine:placebo) to receive three doses of either the HPV-16/18 AS04-adjuvanted vaccine (HPV group), or $Al(OH)_3$ placebo (ALU group); administered intramuscularly according to a 0, 1, and 6 months schedule. Study participants were to have a negative urine pregnancy test before each vaccination and agree to use adequate contraceptive precautions over the vaccination period. Women were excluded from participating in the study if they had used any investigational or non-registered drug or vaccine, were pregnant or lactating or planning/ likely to conceive during the study. Additionally, subjects with a history of HPV vaccination, monophosphoryl lipid A (MPL) or AS04-adjuvant administration, and those with a history of chronic diseases such as autoimmune diseases or cancer were also excluded from study participation.

The study was conducted in accordance with Good Clinical Practice guidelines and adhered to all applicable regulatory requirements, including the Declaration of Helsinki. The study protocol and informed consent documentation were approved by the Independent Ethics Committee or Institutional Review Board of each study centre. All participants and/or parents/ guardians of the participants provided written informed consent/assent prior to conduct and performance of any study-related procedures.

2. Vaccine composition

Each dose of the HPV-16/18 vaccine contained 20 μg each of HPV-16 and -18 L1 (structural protein of HPV) virus like particle and adjuvanted with the proprietary immunostimulatory AS04 adjuvant system (comprising 3-O desacyl-4'-MPL [50 μg] adsorbed on aluminium hydroxide [$Al(OH)_3$, 500 μg]) [18]. The placebo contained 500 μg of aluminium as $Al(OH)_3$ without any viral antigen.

The HPV-16/18 AS04-adjuvanted cervical cancer vaccine was

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developed and manufactured by GSK Biologicals, Belgium. The vaccine was supplied in 0.5 mL pre-filled individual syringes.

3. Randomisation sequence and treatment allocation

The randomisation of the study vaccine/placebo was performed at GSK Biologicals, using a standard statistical analysis system programme. Random allocation of participants was done with a 2:1 blocking scheme using an internet based randomisation system (SBIR) at the investigator site. The randomisation algorithm used a minimisation procedure. The blocking system was used to ascertain that balance was maintained between the treatment arms. A single treatment number was utilised in the entire study to identify the vaccine doses to be administered to the participant.

All participants and study personnel directly involved in the study conduct were blinded throughout the study until the last subject and last visit and the database was frozen.

4. Immunogenicity assessment

Blood samples (5 mL) were collected before vaccination and one month post-dose 3 to evaluate the antibody response against HPV-16 and HPV-18 using ELISA [22]. The assay cut-off for anti-HPV-16 and anti-HPV-18 antibodies was ≥8 ELISA units/millilitre (EL.U/mL) and ≥7 EL.U/mL, respectively [23].

5. Reactogenicity and safety assessment

Diary cards were given to participants or parents/guardians of the participants on the day of vaccination to record solicited and unsolicited (local/general) symptoms during the 7-day and 30-day post-vaccination follow-up period, respectively.

Solicited local symptoms (pain, redness and swelling at the injection site) and solicited general symptoms (fever, headache, fatigue, gastrointestinal symptoms, myalgia, arthralgia, rash, and urticaria) were recorded during the 7-day follow-up period after each vaccine/placebo dose. The intensity of solicited symptoms was graded on a scale of 0-3 based on the extent of discomfort experienced by the participants. Grade 3 (severe) symptoms were defined as: pain that prevented normal day-to-day activity, redness or swelling with an injection site diameter greater than 50 mm, temperature higher than 39°C as fever, urticaria distributed on at least four body areas, or an adverse event (AE) that prevented normal activities. Post-vaccination reactions (urticaria or rash that appeared within 30 minutes of each vaccine dose) were also documented immediately by the investigator. Each solicited AEs and unsolicited AEs were tabulated with exact 95% confidence intervals (CIs) for all vaccine doses and overall.

Serious adverse events (SAEs), new onset chronic diseases (NOCDs) such as autoimmune diseases, asthma, type I diabetes and allergies, other medically significant conditions (MSCs) and pregnancy/pregnancy outcomes were recorded throughout the study period. An event was considered to be an NOCD if it had not been recorded in the previous medical history of the participants' vaccination (i.e., new onset); MSCs were defined as prompting an emergency room, or a physician visit that is unrelated to common diseases or routine visits for physical examination or vaccination, or SAEs unrelated to common diseases.

6. Statistical analysis

Primary analysis of immunogenicity was performed on the according-to-protocol (ATP) cohort, which included all evaluable participants (those meeting all eligibility criteria, complying with protocol defined procedures, without elimination criteria during the study) for whom immunogenicity data were available. The primary analysis of safety was done on the total vaccinated cohort that included all participants with at least one vaccine/placebo dose administered.

A sample size of 120 evaluable participants in the HPV group was required to demonstrate, with at least 92% power, that seroconversion rates for HPV-16 and -18 one month post-dose 3 were not less than 90%. The power calculation was based on a one-sided exact test for one binomial population, type I error of 2.5% with the Bonferroni adjustment of beta using PASS2005 (NCSS, Kaysville, UT, USA).

Seroconversion/seropositivity rates for anti-HPV-16 and anti-HPV-18 antibodies were calculated with their 95% CI. Seroconversion was defined as the appearance of antibodies (i.e., titre ≥cut-off value) in the serum of subjects who are seronegative before vaccination. A seropositive subject was one whose serum antibody titres were ≥cut-off value prior to vaccination. Geometric mean titres (GMTs) with 95% CI and antibody titres range were also tabulated. GMT calculations were performed by taking the anti-log of the mean of the log antibody titres transformations. Antibody titres below the assay cut-off were given an arbitrary value of half the cut-off for GMT calculation.

All statistical analysis was performed using SAS ver. 9.1 (SAS Inc., Cary, NC, USA) programme and Proc StatXact ver. 7.0 (Cytel Inc., Cambridge, MA, USA) software.

RESULTS

1. Study population

The study groups are outlined in (Fig. 1). A total of 225 women

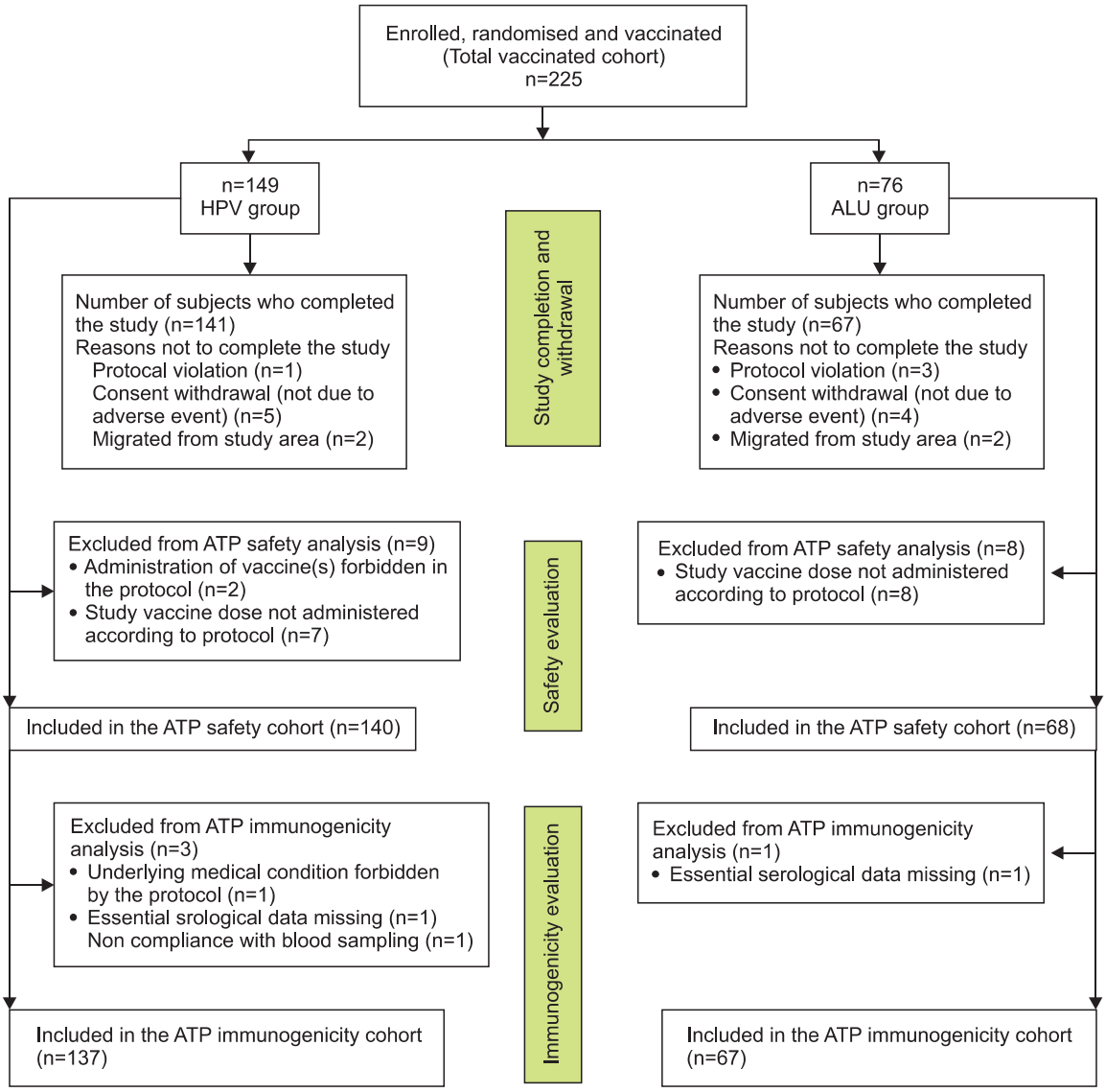

Fig. 1. Study participants flowchart. N, total number of subjects; n, number of subjects with elimination code assigned excluding ones who have been assigned a lower elimination code number.

Table 1. Baseline serological status (ELISA) (total vaccinated cohort)

HPV-16	HPV-18	HPV group (N=149)	ALU group (N=76)	ALL (N=225)
Seropositive	Seropositive	3 (2.1)	1 (1.3)	4 (1.8)
Seropositive	Seronegative	8 (5.5)	5 (6.6)	13 (5.9)
Seronegative	Seropositive	10 (6.8)	7 (9.2)	17 (7.7)
Seronegative	Seronegative	125 (85.6)	63 (82.9)	188 (84.7)
Serology not available for at least one vaccine antigen		3 (-)	0 (-)	3 (-)

HPV group, subjects who received the HPV-16/18 L1 VLP AS04-adjuvanted vaccine; ALU group, subjects who received $Al(OH)_3$; N, number of subjects in each group; n (%), number/percentage of subjects in the considered category.

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were enrolled of whom 208 completed the study (141 in the HPV group and 67 in the ALU group). The ATP safety cohort consisted of 208 women (140 in the HPV group and 68 in the ALU group). The ATP cohort for immunogenicity included 204 women (137 in the HPV group and 67 in the ALU group) (Fig. 1). The mean age of women was 22±2.37 years (total vaccinated cohort). All of them were Asian with East Asian Heritage.

2. Immunogenicity

Seropositivity status at baseline was similar in the two groups. Of the women in the total vaccinated cohort, 85.6% in the HPV group and 82.9% in the ALU group were seronegative for both HPV-16 and -18 antibodies before vaccination (Table 1).

In the ATP immunogenicity cohort, initially seronegative women in the HPV-16/18 group showed 100% seroconversion for anti-HPV-16 and anti-HPV-18 antibodies at one month

Table 2. Immune response to HPV-16 (according-to-protocol cohort for immunogenicity)

Group	Pre-vaccination status	Timing	No.	≥8 EL.U/mL % (95% CI)	GMT (95% CI)
HPV	Seronegative	Pre-vaccination	125	0 (0.0-2.9)	4 (4.0-4.0)
		One month post-dose 3	125	100 (97.1-100)	9,351.4 (8,145.5-1,0735.8)
	Seropositive	Pre-vaccination	11	100 (71.5-100)	23 (12.2-43.3)
		One month post-dose 3	11	100 (71.5-100)	7,918.1 (4,683.5-13,386.7)
	Total	Pre-vaccination	136	8.1 (4.1-14.0)	4.6 (4.2-5.1)
		One month post-dose 3	136	100 (97.3-100)	9,226.4 (8,085.4-10,528.4)
ALU	Seronegative	Pre-vaccination	61	0 (0.0-5.9)	4 (4.0-4.0)
		One month post-dose 3	61	3.3 (0.4-11.3)	4.1 (3.9-4.3)
	Seropositive	Pre-vaccination	6	100 (54.1-100)	33.2 (14.9-73.8)
		One month post-dose 3	6	83.3 (35.9-99.6)	28.8 (9.2-89.6)
	Total	Pre-vaccination	67	9.0 (3.4-18.5)	4.8 (4.1-5.7)
		One month post-dose 3	67	10.4 (4.3-20.3)	4.9 (4.2-5.8)

HPV, subjects who received the HPV-16/18 L1 VLP AS04-adjuvanted vaccine; ALU, subjects who received $Al(OH)_3$; Seronegative, subjects with antibody titre <8 ELISA unit (EL.U)/mL prior to vaccination; Seropositive, subjects with antibody titre ≥8 EL.U/mL prior to vaccination; N, number of subjects with pre-vaccination results available in each group; % (95%CI), percentage of subjects with concentration ≥ specified cut-off with exact 95% confidence interval.

Table 3. Immune response to HPV-18 (according-to-protocol cohort for immunogenicity)

Group	Pre-vaccination status	Timing	No.	≥7 EL.U/mL % (95% CI)	GMT (95% CI)
HPV	Seronegative	Pre-vaccination	122	0 (0.0-3.0)	3.5 (3.5-3.5)
		One month post-dose 3	122	100 (97.0-100)	4,204.1 (3,626.5-4,873.6)
	Seropositive	Pre-vaccination	13	100 (75.3-100)	16.3 (9.5-27.8)
		One month post-dose 3	13	100 (75.3-100)	4,595.0 (2,970.2-7,108.5)
	Total	Pre-vaccination	135	9.6 (5.2-15.9)	4.1 (3.7-4.4)
		One month post-dose 3	135	100 (97.3-100)	4,240.2 (3,692.1-4,869.7)
ALU	Seronegative	Pre-vaccination	61	0 (0.0-5.9)	3.5 (3.5-3.5)
		One month post-dose 3	60	5.0 (1.0-13.9)	3.8 (3.4-4.3)
	Seropositive	Pre-vaccination	6	100 (54.1-100)	15.6 (5.6-43.1)
		One month post-dose 3	6	83.3 (35.9-99.6)	14.1 (5.1-38.6)
	Total	Pre-vaccination	67	9.0 (3.4-18.5)	4 (3.5-4.5)
		One month post-dose 3	66	12.1 (5.4-22.5)	4.3 (3.7-5.0)

HPV, subjects who received the HPV-16/18 L1 VLP AS04-adjuvanted vaccine; ALU, subjects who received $Al(OH)_3$; Seronegative, subjects with antibody titre <7 ELISA unit (EL.U)/mL prior to vaccination; Seropositive, subjects with antibody titre ≥7 EL.U/mL prior to vaccination; N, number of subjects with pre-vaccination results available in each group; % (95%CI), percentage of subjects with concentration ≥ specified cut-off with exact 95% confidence interval.

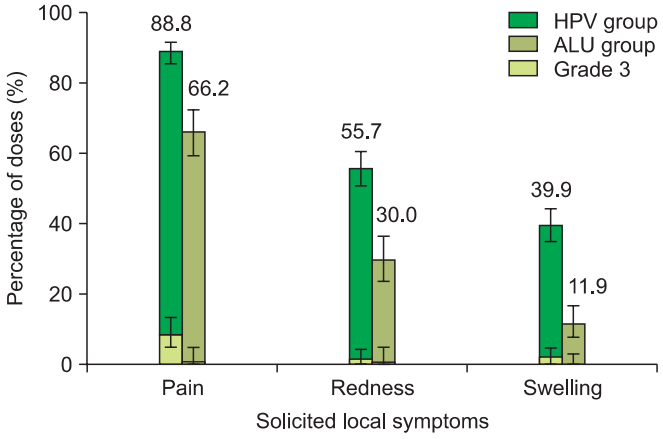

Fig. 2. Solicited local symptoms (overall/dose) with 95% confidence interval during the 7-day post-vaccination period (total vaccinated cohort). HPV group: N=429, ALU group: N=210.

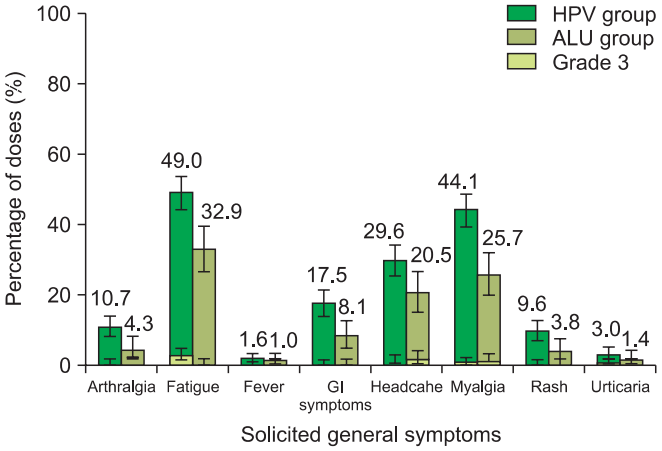

Fig. 3. Solicited general symptoms reported overall/dose during the 7-day post-vaccination period (total vaccinated cohort). HPV group: N=429, ALU group: N=210.

post-dose 3. All initially seropositive women remained seropositive for HPV-16 and/or HPV-18 antibodies one month post-dose 3 in the HPV group (Tables 2 and 3).

GMTs in the HPV group in the initially seronegative and seropositive women were 9,351.4 El.U/mL (95% CI, 8,145.5 to 10,735.8) and 7,918.1 El.U/mL (95% CI, 4,683.5 to 13,386.7) for anti-HPV-16 antibodies and 4,204.1 El.U/mL (95% CI, 3,626.5 to 4,873.6) and 4,595.0 El.U/mL (95% CI, 2,970.2 to 7,108.5) for anti-HPV-18 antibodies, respectively, one month post-dose 3. GMTs for initially seronegative and seropositive women in the ALU group are shown in (Tables 2 and 3).

3. Safety and reactogenicity (total vaccinated cohort)

The compliance rate with respect to returning the diary cards were similar in the HPV group (98.4%) and the ALU group (97.2%).

1) Solicited local and general AEs

Solicited local symptoms were reported more frequently in the HPV group than the ALU group. Pain at the injection site was the most frequently reported local symptom in both groups (Fig. 2). Grade 3 symptoms were rarely reported in both groups (pain reported after 4.4% of doses in the HPV group, redness and swelling after 0.9% and 1.2% of doses in the HPV group). In the ALU group, grade 3 symptoms were reported following ≤0.5% of doses. Most of these local symptoms were transient with a mean duration of 3.4-3.7 days for each symptom in the HPV group and 2.3-2.4 days in the ALU group.

During the 7-day post-vaccination follow-up period, the occurrence of fatigue, myalgia and headache was frequent in both groups. Fatigue, myalgia and gastrointestinal symptoms were recorded more frequently in the HPV group than the ALU group (overall/dose) (Fig. 3). Grade 3 symptoms reported were generally low across both groups (not exceeding 2.8% of doses in the HPV group). In the ALU group, grade 3 symptoms were not reported except for headache (after 1.4% of doses) and myalgia (after 1.0% of doses) (Fig. 3). The mean duration of solicited general symptoms was 2.1-3.0 days in the HPV group, lasting longer for arthralgia, myalgia, rash and urticaria. In the ALU group, the mean duration was 1.0-2.6 days. None of the subjects reported urticaria or rash in the 30-minute post-vaccination period in both groups.

Compliance to the 3-dose vaccination course was high (95.3% of women in the HPV group [n=142] and 89.5% of women in the ALU group [n=68] [total vaccinated cohort]).

2) Unsolicited adverse events, MSCs, NOCDs, SAEs, and pregnancy

Unsolicited AEs were reported after 20.4% (95% CI, 16.7 to 24.5) of doses in the HPV group (number of administered doses, 436) and after 10.2% (95% CI, 6.5 to 15.0) of doses in the ALU group (number of administered doses, 216). Infections and infestations (after 6.9% of doses in the HPV group and 3.2% of doses in the ALU group overall) followed by breast and reproductive system disorders (after 3.7% of doses in the HPV group and 1.4% of doses in the ALU group overall) were the most frequently reported symptoms in both groups. No imbalance in the incidence of any individual unsolicited symptoms was identified between the two groups. Grade 3 unsolicited AEs were reported after 0.9% of doses in the HPV group (gastrointestinal disorder, vomiting, pain, upper respiratory tract infection, and dizziness), and after 0.5% of doses in the ALU group (injection site warmth and malaise).

At least one medically significant adverse condition was

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reported by 22.8% of women in the HPV group and 13.2% of women in the ALU group. Gastrointestinal disorders and skin and subcutaneous tissue disorders were the most commonly reported in both groups. Eleven women (five [3.4%] in the HPV group and six [7.9%] in the ALU group) reported at least one NOCD in the study (GSK assessment based on pre-defined list).

Three non-fatal SAEs (gastroenteritis viral, pelvic inflammatory disease, and ruptured ovarian cyst) were reported during the study (two in the HPV group and one in the ALU group). The investigator did not consider these to be related to vaccination and they all recovered. One pregnancy was reported in the ALU group during the study. This woman opted for elective abortion after 12 weeks of pregnancy due to personal reasons.

DISCUSSION

Despite regular cytology screening becoming an effective tool in cervical cancer prevention, cervical cancer continues to pose a considerable threat in the developing parts of the world [24,25]. Although Korea is no longer a developing country, the incidence and mortality rate of cervical cancer in Korea suggests that cervical cancer is still a major health concern in the region [2,3]. Two studies which included Korean adolescents aged 10-14 years have been conducted previously to evaluate the immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine [26,27]. The present study was conducted in Korean girls 15-25 years of age.

In the present study, all women initially seronegative for anti-HPV-16 and -18 antibodies seroconverted at one month post-dose 3, with high antibody titres achieved against both antigens. Initially seropositive women exhibited comparable GMTs one month post-dose 3 as in the initially seronegative women. The GMT levels in the current study were at least 180 fold higher for both antigens one month post-dose 3 than those observed after natural infection with HPV-16/18 [16]. The level of protection conferred and the immunity induced following a natural infection are unknown. However, it is shown that not all women develop serum antibodies to HPV after a natural infection [28], and because antibodies after a natural infection are relatively low and do not reliably protect against re-infection, women who may have already been exposed to the infection are still susceptible to re-infection. Vaccination with the HPV-16/18 AS04-adjuvanted cervical cancer vaccine helps in inducing sustained antibody responses. The high immunogenicity, the role of novel AS04-adjuvant in the induction of high immune response and its implications have been shown and elaborated in a previous study in Korean pre-teens and young adolescents aged 10-14 years [27]. Immunological superiority of the AS04-adjuvanted formulation has been observed before when compared to the same antigens adjuvanted with aluminium alone [29,30].

Although the current study did not evaluate the efficacy of the vaccine, in a large international phase III study across 14 countries in women from 15-25 years of age (same age range as this study) [13,16], the HPV-16/18 AS04-adjuvanted vaccine has demonstrated to be highly efficacious against infections and CIN2+ lesions associated with HPV-16 and HPV-18, with additional cross-protection against persistent infections and cervical lesions with other oncogenic non-vaccine types (i.e., HPV -31, HPV-33, and HPV-45). Magnitude of immune response (GMTs) achieved in this study was similar to that observed in the above global trial, and comparable to other HPV trials in women in Asia, Europe and North America, which indicates no ethnic differences, and similar efficacy can be expected in Korean women 15-25 years of age.

Although the study was not powered for safety evaluation, safety data generated in this study are similar to those shown in other global studies [13-17]. Incidence of local injection site symptoms and some general symptoms was observed to be higher in the HPV group than in the ALU group, with grade 3 local and general symptoms being rare in both groups. The majority of AEs were generally mild and resolved within a couple of days, and compliance with vaccinations was high with over 90% women completing the full vaccination schedule. This is in line with the clinical experience with AS04-adjuvanted formulations confirming the HPV-16/18 AS04-adjuvanted vaccine to have a clinically acceptable safety profile in Korean women.

A rapid change is being observed in the sexual behaviour and social activity in Korea, with sexual debut becoming earlier in Korean women. This change has led to an increased risk of HPV infection in Korean women, which in turn has increased the incidence of cervical cancer in this region, as confirmed by two surveys conducted in Busan, Korea [31,32]. Cervical cancer screening using the Papanicolaou test has helped in a considerable reduction in cervical cancer burden in Korea since its introduction in the 1950s in the region by the Korean Government [2,25]. Regular screening has shown to reduce the ICC incidence in a prospective cohort study in Korea [33]. However, participation of women in such screening programmes is shown to be marked by socioeconomic inequality, largely dependent on the socioeconomic status of women [34]. Hence, immunisation of adolescents and young women before sexual debut can help in providing early protection as depicted in a previous study of Korean

population of 10-14 years of age [27], to complement the cervical cancer screening programme. Additional measures of increased disease awareness amongst young women and about the risks and benefits of vaccination and age-based interventions policy programmes can further facilitate to control the cervical cancer burden in Korea [2,25].

In conclusion, the HPV-16/18 AS04-adjuvanted cervical cancer vaccine was shown to be highly immunogenic and has a clinically acceptable safety profile in the Korean population of 15-25 year olds, as previously shown in a Korean population of 10-14 year old adolescents and girls in another study. With cervical cancer being a major health problem in Korean women, prophylactic HPV vaccination may be integrated into routine immunisation programmes, in line with recommendations by the WHO, to help combat the cervical cancer disease burden.

CONFLICT OF INTEREST

Dan Bi is an employee, and also owns shares of GlaxoSmithKline Biologicals, which is the sponsor of this study. Bhavyashree Gunapalaiah and Hans L Bock were employed at GlaxoSmithKline at the time of study design, conduct and manuscript development. However, they have since left the company. Young Tae Kim had received consulting fees/honoraria from GlaxoSmithKline in the past three years. The other authors declare that they do not have any conflict of interest.

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