Clinical trial results:
A post-marketing surveillance (PMS) study to monitor the safety and reactogenicity of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine (Cervarix) in 3,000 healthy female Filipino subjects when administered according to the Prescribing Information from the age of 10 years onwards.

Summary

EudraCT number	2017-000458-20
Trial protocol	Outside EU/EEA
Global end of trial date	16 January 2012

Results information

Result version number	v1
This version publication date	24 February 2018
First version publication date	24 February 2018

Trial information

Trial identification

Sponsor protocol code	108160

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00730847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2012
Global end of trial reached?	Yes
Global end of trial date	16 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and reactogenicity of GlaxoSmithKline Biologicals' human papillomavirus vaccine (Cervarix) in 3,000 healthy female Filipino subjects.

Protection of trial subjects:

All subjects were observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Philippines: 743
Worldwide total number of subjects	743
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	143
Adolescents (12-17 years)	300
Adults (18-64 years)	300
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Since this was a post-marketing study (PMS), subjects may have received one or two doses of Cervarix outside of the PMS.

Pre-assignment

Screening details:

Out of 743 subjects enrolled in the study, only 596 subjects received study vaccination.
The whole set of data was not cleaned for this study. Analysis was performed on subjects with cleaned data and on subjects with missing data or unresolved data queries, or both. The overall group includes both cleaned and not cleaned data.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was conducted in an open manner.

Arms

Arm title	Cervarix Group

Arm description:

Healthy female subjects who received three doses of Cervarix vaccine administered intramuscularly in the deltoid region according to a 0, 1 and 6-month schedule.

Arm type	Experimental
Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	HPV-16/18 VLP/AS04 vaccine
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

All subjects were administered a 0.5 mL dose of the vaccine as an intramuscular injection in the deltoid region, according to a 0, 1 and 6-month schedule.

Number of subjects in period 1[1]	Cervarix Group
Started	596
Completed	465
Not completed	131
Consent withdrawn by subject	16
Adverse event, non-fatal	1
Unspecified	24
Lost to follow-up	67
Protocol deviation	2
Unknown completion status	21

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 743 subjects enrolled in the study, only 596 subjects received study vaccination.

Baseline characteristics

Reporting groups	
Reporting group title	Cervarix Group
Reporting group description:	
Healthy female subjects who received three doses of Cervarix vaccine administered intramuscularly in the deltoid region according to a 0, 1 and 6-month schedule.	

Reporting group values	Cervarix Group	Total	
Number of subjects	596	596	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	32.8		
standard deviation	± 10.27	-	
Gender categorical Units: Subjects			
Female	596	596	
Male	0	0	
Race/Ethnicity Units: Subjects			
South Asian	594	594	
Chinese	1	1	
Not specified	1	1	

End points

End points reporting groups

Reporting group title	Cervarix Group

Reporting group description:

Healthy female subjects who received three doses of Cervarix vaccine administered intramuscularly in the deltoid region according to a 0, 1 and 6-month schedule.

Primary: Number of subjects reporting any and Grade 3 solicited local symptoms

End point title	Number of subjects reporting any and Grade 3 solicited local symptoms[1]

End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was defined as any solicited local symptom reported irrespective of intensity grade. Grade 3 pain was defined as pain that prevented normal activity. Grade 3 redness and swelling were defined as redness and swelling above 50 millimeters (mm).

End point type	Primary

End point timeframe:

During the 7-day follow-up period (Days 0-6) after each dose and across doses

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	578			
Units: Subjects				
Any Pain, Dose 1 (N=576)	402			
Grade 3 Pain, Dose 1 (N=576)	25			
Any Redness, Dose 1 (N=576)	116			
Grade 3 Redness, Dose 1 (N=576)	0			
Any Swelling, Dose 1 (N=576)	76			
Grade 3 Swelling, Dose 1 (N=576)	3			
Any Pain, Dose 2 (N=531)	309			
Grade 3 Pain, Dose 2 (N=531)	16			
Any Redness, Dose 2 (N=531)	106			
Grade 3 Redness, Dose 2 (N=531)	0			
Any Swelling, Dose 2 (N=531)	60			
Grade 3 Swelling, Dose 2 (N=531)	0			
Any Pain, Dose 3 (N=482)	211			
Grade 3 Pain, Dose 3 (N=482)	7			
Any Redness, Dose 3 (N=482)	69			
Grade 3 Redness, Dose 3 (N=482)	2			
Any Swelling, Dose 3 (N=482)	47			
Grade 3 Swelling, Dose 3 (N=482)	1			
Any Pain, Across Doses (N=578)	430			
Grade 3 Pain, Across Doses (N=578)	38			
Any Redness, Across Doses (N=578)	168			

Grade 3 Redness, Across Doses (N=578)	2			
Any Swelling, Across Doses (N=578)	119			
Grade 3 Swelling, Across Doses (N=578)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting any, Grade 3 and related solicited general symptoms

End point title	Number of subjects reporting any, Grade 3 and related solicited general symptoms[2]

End point description:

Solicited general symptoms assessed were arthralgia, fatigue, fever, gastrointestinal, headache, myalgia, rash and urticaria. Any fever = axillary temperature ≥ 37.5 degrees Celsius (°C). For other symptoms: Any = any solicited general symptom reported irrespective of intensity and relationship to study vaccination. Related = symptoms considered by the investigator as causally related to study vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Grade 3 urticaria = urticaria distributed on at least 4 body areas. Grade 3 fever = axillary temperature > 39.0°C.

End point type	Primary

End point timeframe:

During the 7-day follow-up period (Days 0-6) after each dose and across doses

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	576			
Units: Subjects				
Any Arthralgia, Dose 1 (N=575)	76			
Grade 3 Arthralgia, Dose 1 (N=575)	2			
Related Arthralgia, Dose 1 (N=575)	35			
Any Fatigue, Dose 1 (N=575)	120			
Grade 3 Fatigue, Dose 1 (N=575)	4			
Related Fatigue, Dose 1 (N=575)	53			
Any Fever, Dose 1 (N=575)	17			
Grade 3 Fever, Dose 1 (N=575)	1			
Related Fever, Dose 1 (N=575)	7			
Any Gastrointestinal, Dose 1 (N=575)	46			
Grade 3 Gastrointestinal, Dose 1 (N=575)	3			
Related Gastrointestinal, Dose 1 (N=575)	10			
Any Headache, Dose 1 (N=575)	90			
Grade 3 Headache, Dose 1 (N=575)	3			
Related Headache, Dose 1 (N=575)	29			
Any Myalgia, Dose 1 (N=575)	91			
Grade 3 Myalgia, Dose 1 (N=575)	4			

Related Myalgia, Dose 1 (N=575)	39			
Any Rash, Dose 1 (N=575)	9			
Grade 3 Rash, Dose 1 (N=575)	0			
Related Rash, Dose 1 (N=575)	4			
Any Urticaria, Dose 1 (N=575)	8			
Grade 3 Urticaria, Dose 1 (N=575)	0			
Related Urticaria, Dose 1 (N=575)	3			
Any Arthralgia, Dose 2 (N=529)	43			
Grade 3 Arthralgia, Dose 2 (N=529)	1			
Related Arthralgia, Dose 2 (N=529)	15			
Any Fatigue, Dose 2 (N=529)	81			
Grade 3 Fatigue, Dose 2 (N=529)	6			
Related Fatigue, Dose 2 (N=529)	35			
Any Fever, Dose 2 (N=529)	11			
Grade 3 Fever, Dose 2 (N=529)	0			
Related Fever, Dose 2 (N=529)	9			
Any Gastrointestinal, Dose 2 (N=529)	32			
Grade 3 Gastrointestinal, Dose 2 (N=529)	1			
Related Gastrointestinal, Dose 2 (N=529)	9			
Any Headache, Dose 2 (N=529)	55			
Grade 3 Headache, Dose 2 (N=529)	3			
Related Headache, Dose 2 (N=529)	20			
Any Myalgia, Dose 2 (N=529)	52			
Grade 3 Myalgia, Dose 2 (N=529)	2			
Related Myalgia, Dose 2 (N=529)	20			
Any Rash, Dose 2 (N=529)	7			
Grade 3 Rash, Dose 2 (N=529)	1			
Related Rash, Dose 2 (N=529)	3			
Any Urticaria, Dose 2 (N=529)	6			
Grade 3 Urticaria, Dose 2 (N=529)	1			
Related Urticaria, Dose 2 (N=529)	1			
Any Arthralgia, Dose 3 (N=481)	30			
Grade 3 Arthralgia, Dose 3 (N=481)	3			
Related Arthralgia, Dose 3 (N=481)	13			
Any Fatigue, Dose 3 (N=481)	57			
Grade 3 Fatigue, Dose 3 (N=481)	3			
Related Fatigue, Dose 3 (N=481)	28			
Any Fever, Dose 3 (N=481)	12			
Grade 3 Fever, Dose 3 (N=481)	0			
Related Fever, Dose 3 (N=481)	8			
Any Gastrointestinal, Dose 3 (N=481)	15			
Grade 3 Gastrointestinal, Dose 3 (N=481)	0			
Related Gastrointestinal, Dose 3 (N=481)	6			
Any Headache, Dose 3 (N=481)	39			
Grade 3 Headache, Dose 3 (N=481)	2			
Related Headache, Dose 3 (N=481)	13			
Any Myalgia, Dose 3 (N=481)	30			
Grade 3 Myalgia, Dose 3 (N=481)	1			
Related Myalgia, Dose 3 (N=481)	13			

Any Rash, Dose 3 (N=481)	4			
Grade 3 Rash, Dose 3 (N=481)	1			
Related Rash, Dose 3 (N=481)	2			
Any Urticaria, Dose 3 (N=481)	2			
Grade 3 Urticaria, Dose 3 (N=481)	0			
Related Urticaria, Dose 3 (N=481)	0			
Any Arthralgia, Across doses (N=576)	102			
Grade 3 Arthralgia, Across doses (N=576)	6			
Related Arthralgia, Across doses (N=576)	48			
Any Fatigue, Across doses (N=576)	165			
Grade 3 Fatigue, Across doses (N=576)	11			
Related Fatigue, Across doses (N=576)	72			
Any Fever, Across doses (N=576)	32			
Grade 3 Fever, Across doses (N=576)	1			
Related Fever, Across doses (N=576)	19			
Any Gastrointestinal, Across doses (N=576)	68			
Grade 3 Gastrointestinal, Across doses (N=576)	4			
Related Gastrointestinal, Across doses (N=576)	19			
Any Headache, Across doses (N=576)	127			
Grade 3 Headache, Across doses (N=576)	6			
Related Headache, Across doses (N=576)	47			
Any Myalgia, Across doses (N=576)	115			
Grade 3 Myalgia, Across doses (N=576)	7			
Related Myalgia, Across doses (N=576)	51			
Any Rash, Across doses (N=576)	17			
Grade 3 Rash, Across doses (N=576)	2			
Related Rash, Across doses (N=576)	8			
Any Urticaria, Across doses (N=576)	14			
Grade 3 Urticaria, Across doses (N=576)	1			
Related Urticaria, Across doses (N=576)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting any, Grade 3, related, and Grade 3 and related unsolicited adverse events (AEs)

End point title	Number of subjects reporting any, Grade 3, related, and Grade 3 and related unsolicited adverse events (AEs)[3]

End point description:

An unsolicited AE covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to study vaccination. Grade 3 = event which prevented normal, everyday activities. Related = event assessed by the investigators as causally related to the study vaccination. Grade 3 and Related = grade 3 event assessed by the investigators as causally related to the study vaccination.

End point type	Primary

End point timeframe:

During the 30-day (Days 0-29) post-vaccination period

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	596			
Units: Subjects				
Any AE(s)	20			
Grade 3 AE(s)	3			
Related AE(s)	2			
Grade 3 and Related AE(s)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with any, Grade 3 and related serious adverse events (SAEs)

End point title	Number of subjects with any, Grade 3 and related serious adverse events (SAEs)[4]

End point description:

SAEs assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization, resulted in disability/incapacity or were a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence of any symptom regardless of intensity grade. Grade 3 SAE = SAE which prevented normal, everyday activities. Related SAE = SAE assessed by the investigator as causally related to the study vaccination.

End point type	Primary

End point timeframe:

During the entire study period (from Day 0 up to Month 7)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	596			
Units: Subjects				
Any SAE(s)	4			
Grade 3 SAE(s)	1			
Related SAE(s)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited local and general symptoms: during the 7-day (Days 0-6) post-vaccination period; Unsolicited adverse events: during the 30-day (Days 0-29) post-vaccination period; Serious adverse events: during the entire study period (from Day 0 up to Month 7)

Adverse event reporting additional description:

For the systematically assessed other (non-serious) adverse events, the number of participants at risk included those from Total Vaccinated cohort who had the symptom sheet completed. No related SAEs were reported and one (Uterine leiomyoma) was assessed as severe (Grade 3).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Cervarix Group

Reporting group description:

Healthy female subjects who received three doses of Cervarix vaccine administered intramuscularly in the deltoid region according to a 0, 1 and 6-month schedule.

Serious adverse events	Cervarix Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 596 (0.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Mitral valve prolapse			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Typhoid fever			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cervarix Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	443 / 596 (74.33%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	127 / 596 (21.31%)		
occurrences (all)	184		
General disorders and administration site conditions			

Chills subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		
Fatigue subjects affected / exposed occurrences (all)	165 / 596 (27.68%) 258		
Injection site erythema subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		
Pain subjects affected / exposed occurrences (all)	430 / 596 (72.15%) 922		
Pyrexia subjects affected / exposed occurrences (all)	32 / 596 (5.37%) 42		
Swelling subjects affected / exposed occurrences (all)	119 / 596 (19.97%) 183		
Gastrointestinal disorders Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		
Gastrointestinal disorder subjects affected / exposed occurrences (all)	68 / 596 (11.41%) 93		
Reproductive system and breast disorders Polycystic ovaries subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		

Cough			
subjects affected / exposed	4 / 596 (0.67%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	168 / 596 (28.19%)		
occurrences (all)	291		
Pruritus			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	17 / 596 (2.85%)		
occurrences (all)	20		
Urticaria			
subjects affected / exposed	14 / 596 (2.35%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	102 / 596 (17.11%)		
occurrences (all)	149		
Back pain			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	115 / 596 (19.30%)		
occurrences (all)	173		
Infections and infestations			
Herpes zoster			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 596 (0.17%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 596 (0.34%)		
occurrences (all)	2		

Urinary tract infection subjects affected / exposed occurrences (all)	7 / 596 (1.17%) 7		
Vaginitis bacterial subjects affected / exposed occurrences (all)	1 / 596 (0.17%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2008	- The mandated telephone call to be done on Day 8 as a study procedure has been removed from relevant sections as the procedure was deemed as an extra obligation beyond the normal clinical practice for the investigators as per local customs. Instead, investigators have to emphasize to the subjects on the day of visit itself that they should monitor for AEs, complete their diary card, and return it at their next visit. - The indication/study population has been updated to reflect the indication in the approved PI. - The licensure of the Cervarix in the European Union has been added in Section 1.2 to provide updated information. - No blood samples were planned to be collected. In case an autoimmune disease is diagnosed during the study, autoantibody testing may be performed on blood samples collected (approximately 1mL), if agreed by the subject (see Section 8.4). - Changes were done to Section 4.2 to reflect updates in the protocol over versions 12.3, 12.4 and 12.5 related to adequate contraception for participation in the study. Section 5.2.1 has been added to include protocol version upgrades related to adequate contraception (SOP-WWD-0015). Section 6.6 (Concomitant medication/treatment) has also been updated to reflect changes from versions 12.3, 12.4 and 12.5. - The Clinical Research Associates (CRAs) contributing to authoring have been updated in the title page and the details of study contact for reporting SAEs have been updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported