Clinical trial results:
A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study.

Summary

EudraCT number	2010-020227-48
Trial protocol	PT
Global end of trial date	10 January 2017

Results information

Result version number	v1 (current)
This version publication date	07 January 2018
First version publication date	07 January 2018

Trial information

Trial identification

Sponsor protocol code	113618

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01249365
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 Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2017
Global end of trial reached?	Yes
Global end of trial date	10 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of the HPV-16/18 L1 VLP AS04 vaccine throughout the study period.

Protection of trial subjects:

The vaccinees were observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccine.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Portugal: 54
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Singapore: 81
Worldwide total number of subjects	199
EEA total number of subjects	54

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	196

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 16 centers in total, located in 4 countries: Australia, Portugal, Russian Federation and Singapore.

Pre-assignment

Screening details:

All subjects were included in the trial.

Period 1

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

Arms

Arm title	HPV vaccine

Arm description:

Healthy female subjects aged 26 years and above, who received control vaccine in the primary study NCT00294047, were administrated 3 intramuscular injections of Cervarix vaccine into the deltoid of the non-dominant arm, according to a 0, 1, 6-month schedule in the current study.

Arm type	Experimental
Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received three doses of the study vaccine administered intramuscularly according to a 0, 1, 6-month schedule.

Number of subjects in period 1	HPV vaccine
Started	199
Completed	198
Not completed	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	HPV vaccine

Reporting group description:

Healthy female subjects aged 26 years and above, who received control vaccine in the primary study NCT00294047, were administrated 3 intramuscular injections of Cervarix vaccine into the deltoid of the non-dominant arm, according to a 0, 1, 6-month schedule in the current study.

Reporting group values	HPV vaccine	Total	
Number of subjects	199	199	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 46.9 ± 7.2	 -	
Gender categorical Units: Subjects			
Female	199	199	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
African Heritage/African American	1	1	
Asian - Central/South Asian Heritage	2	2	
Asian - East Asian Heritage	2	2	
Asian - South East Asian Heritage	78	78	
White - Caucasian/European Heritage	116	116	

End points

End points reporting groups

Reporting group title	HPV vaccine

Reporting group description:

Healthy female subjects aged 26 years and above, who received control vaccine in the primary study NCT00294047, were administrated 3 intramuscular injections of Cervarix vaccine into the deltoid of the non-dominant arm, according to a 0, 1, 6-month schedule in the current study.

Primary: Number of subjects reporting serious adverse events

End point title	Number of subjects reporting serious adverse events[1]

End point description:

Serious adverse events (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 the occurrence of any SAE regardless of intensity grade or relation to vaccination. Grade 3 SAE = SAE which prevented normal, everyday activities (in adults/adolescents, such an SAE, for example, prevented attendance at work/school and necessitated the administration of corrective therapy). Related SAE = SAE assessed by the investigator as causally related to the vaccination.

End point type	Primary

End point timeframe:

Throughout the study (from Month 0 to Month 12)

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	HPV vaccine			
Subject group type	Reporting group			
Number of subjects analysed	199			
Units: Subjects				
Any SAE(s)	6			
Grade 3 SAE(s)	2			
Related SAE(s)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting medically significant conditions (MSCs) and potential immune-mediated diseases (pIMDs)

End point title	Number of subjects reporting medically significant conditions (MSCs) and potential immune-mediated diseases (pIMDs)[2]

End point description:

Medically significant conditions (MSCs) are defined as: AEs prompting emergency room or physician visits that were not related to common diseases, or not related to routine visits for physical examination or vaccination; SAEs that were not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury. Potential immune-mediated diseases (pIMDs) are a

subset of medically significant conditions that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. Any was defined as the occurrence of any MSC or pIMD regardless of intensity grade or relation to vaccination. Grade 3 MSC or pIMD = a MSC or pIMD which prevented normal, everyday activities. Related MSC or pIMD = a MSC or pIMD assessed by the investigator as related to the vaccination.

End point type	Primary

End point timeframe:

Throughout the study (from Month 0 to Month 12)

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	HPV vaccine			
Subject group type	Reporting group			
Number of subjects analysed	199			
Units: Subjects				
Any MSCs	16			
Grade 3 MSCs	2			
Related MSCs	0			
Any pIMDs	1			
Grade 3 pIMDs	0			
Related pIMDs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects reporting pregnancies and outcome of reported pregnancies

End point title	Number of subjects reporting pregnancies and outcome of reported pregnancies[3]

End point description:

Live infant NO apparent congenital anomaly; Live infant congenital anomaly; Premature live infant NO apparent congenital anomaly; Premature live infant congenital anomaly; Elective termination NO apparent congenital anomaly; Elective termination congenital anomaly; Therapeutic abortion; Ectopic pregnancy; Spontaneous abortion NO apparent congenital anomaly; Spontaneous abortion congenital anomaly; Stillbirth NO apparent congenital anomaly; Stillbirth congenital anomaly; Molar pregnancy; Pregnancy ongoing; Lost to follow up.
The analysis was based on the Total Vaccinated cohort, which included all subjects with the study vaccine administered and who reported any pregnancies and outcomes of reported pregnancies.

End point type	Primary

End point timeframe:

Throughout the study (from Month 0 to Month 12)

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	HPV vaccine			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Live infant NO apparent congenital anomaly	1			
Live infant congenital anomaly	0			
Premature live infant NO apparent congen. anomaly	0			
Premature live infant congenital anomaly	0			
Elective termination NO apparent congen. anomaly	0			
Elective termination congenital anomaly	0			
Therapeutic abortion	0			
Ectopic pregnancy	0			
Spontaneous abortion NO apparent congen. anomaly	0			
Spontaneous abortion congenital anomaly	0			
Stillbirth NO apparent congenital anomaly	0			
Stillbirth congenital anomaly	0			
Molar pregnancy	0			
Pregnancy ongoing	0			
Lost to follow up	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse Events were reported from the first receipt of study vaccine (Month 0) until 6 months following administration of the last dose of study vaccine (i.e. at study conclusion, Month 12).

Adverse event reporting additional description:

Non-serious solicited adverse events were not collected in this study. Non-serious unsolicited events collected in this study did not exceed the threshold of 5%.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	HPV vaccine

Reporting group description:

Healthy female subjects aged 26 years and above, who received control vaccine in the primary study NCT00294047, were administrated 3 intramuscular injections of Cervarix vaccine into the deltoid of the non-dominant arm, according to a 0, 1, 6-month schedule in the current study.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious solicited adverse events were not collected in this study. Non-serious unsolicited adverse events collected included MSCs and pIMDs, presented previously as a primary endpoint.

Serious adverse events	HPV vaccine		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 199 (3.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve root compression			
subjects affected / exposed	1 / 199 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			

subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Major depression				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Agitated depression				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Post-traumatic stress disorder				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Joint range of motion decreased				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Trigger finger				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 199 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	HPV vaccine		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 199 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2010	Due to their potent immune stimulating effect, there are theoretical concerns that modern adjuvants like GSK Biologicals' novel adjuvant systems might result in undesirable effects on the body's immune system, which could include onset of new or exacerbation of underlying autoimmune diseases in particular. Accordingly, a heightened surveillance on the occurrence of any such conditions in recipients of novel adjuvant containing vaccines in clinical trials has been put in place by GSK. Protocol amendment 1 was hence developed to implement reporting of potential immune-mediated diseases (pIMDs).
13 January 2011	"The exclusion criterion “Administration of any chronic drug therapy to be continued during the study period” has been removed to be in line with the original HPV-015 study protocol. Upon request of regulatory authorities, the list of pIMDs has been updated to include the term “undifferentiated spondyloarthritides”."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported