



Clinical trial results:

A long-term, open, follow-up of the immunogenicity and safety of GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in healthy female subjects up to 10 years after administration of the first vaccine dose in study HPV-014

Summary

EudraCT number	2009-011357-41
Trial protocol	DE PL
Global end of trial date	03 February 2015

Results information

Result version number	v2 (current)
This version publication date	30 November 2020
First version publication date	13 February 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Results have been amended to account for consistency with other registries.

Trial information

Trial identification

Sponsor protocol code	112772
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00947115
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, 044 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 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	11 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 February 2015
Global end of trial reached?	Yes
Global end of trial date	03 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term immunogenicity of the HPV-16/18 vaccine in serum from all subjects by enzyme-linked immunosorbent assay (ELISA) at Years 5, 6, 7, 8, 9 and 10 following first dose of HPV vaccine.

Protection of trial subjects:

All subjects were followed up for reporting of vaccine-, study participation-, or GSK concomitant medication-related SAEs and fatal SAEs.

Data were collected and recorded from the time the subject consented to participate in the study until the end of participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 222
Country: Number of subjects enrolled	Germany: 303
Worldwide total number of subjects	525
EEA total number of subjects	525

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)	525
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at six centers in Germany and Poland.

Pre-assignment

Screening details:

Out of the 525 enrolled subjects, 1 subject was excluded for not receiving vaccination and the actual starting number was 524.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cervarix 15-25 years group

Arm description:

Women, aged 15 to 25 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

Arm type	Active comparator
Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

No vaccine was administered in this extension study. Blood samples from all subjects, and cervico-vaginal secretion (CVS) samples from subjects who volunteered for this procedure, were collected at each study visit (i.e. at Years 5, 6, 7, 8, 9 and 10). Subjects received 3 doses of Cervarix vaccine administered intramuscularly, according to a 0, 1, 6-month vaccination schedule in the primary study HPV-014 (NCT00196937).

Arm title	Cervarix 26-45 years group
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Arm description:

Women, aged 26 to 45 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

Arm type	Active comparator
Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

No vaccine was administered in this extension study. Blood samples from all subjects, and cervico-vaginal secretion (CVS) samples from subjects who volunteered for this procedure, were collected at each study visit (i.e. at Years 5, 6, 7, 8, 9 and 10). Subjects received 3 doses of Cervarix vaccine administered intramuscularly, according to a 0, 1, 6-month vaccination schedule in the primary study HPV-014 (NCT00196937).

Arm title	Cervarix 46-55 years group
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Arm description:

Women, aged 46 to 55 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

Arm type	Active comparator
Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

No vaccine was administered in this extension study. Blood samples from all subjects, and cervico-vaginal secretion (CVS) samples from subjects who volunteered for this procedure, were collected at each study visit (i.e. at Years 5, 6, 7, 8, 9 and 10). Subjects received 3 doses of Cervarix vaccine administered intramuscularly, according to a 0, 1, 6-month vaccination schedule in the primary study HPV-014 (NCT00196937).

Number of subjects in period 1 ^[1]	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group
Started	159	194	171
Completed	142	172	156
Not completed	17	22	15
Adverse event, serious fatal	-	1	1
Missed reporting interval	3	4	2
Consent withdrawn by subject	1	3	4
Physician decision	-	2	-
Migrated from study area	2	-	-
Lost to follow-up	11	12	8

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 the 525 enrolled subjects, 1 subject was excluded for not receiving vaccination and the actual starting number was 524.

Baseline characteristics

Reporting groups

Reporting group title	Cervarix 15-25 years group
Reporting group description: Women, aged 15 to 25 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	
Reporting group title	Cervarix 26-45 years group
Reporting group description: Women, aged 26 to 45 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	
Reporting group title	Cervarix 46-55 years group
Reporting group description: Women, aged 46 to 55 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	

Reporting group values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group
Number of subjects	159	194	171
Age categorical			
(Data for Year 5 - Year 10)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	159	194	171
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
(Data for Year 5 - Year 10)			
Units: years			
arithmetic mean	25.7	41.0	54.4
standard deviation	± 2.82	± 6.02	± 3.15
Sex: Female, Male			
(Data for Year 5 - Year 10)			
Units: Subjects			
Female	159	194	171
Male	0	0	0
Race/Ethnicity, Customized			
(Data for Year 5 - Year 10)			
Units: Subjects			
Black	0	1	0
White/Caucasian	159	193	171

Reporting group values	Total		
Number of subjects	524		
Age categorical			
(Data for Year 5 - Year 10)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	524		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
(Data for Year 5 - Year 10)			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
(Data for Year 5 - Year 10)			
Units: Subjects			
Female	524		
Male	0		
Race/Ethnicity, Customized			
(Data for Year 5 - Year 10)			
Units: Subjects			
Black	1		
White/Caucasian	523		

End points

End points reporting groups

Reporting group title	Cervarix 15-25 years group
Reporting group description: Women, aged 15 to 25 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	
Reporting group title	Cervarix 26-45 years group
Reporting group description: Women, aged 26 to 45 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	
Reporting group title	Cervarix 46-55 years group
Reporting group description: Women, aged 46 to 55 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).	

Primary: Anti-Human Papillomavirus (Anti-HPV)-16/18 antibody titers in serum at years 5, 6 and 7

End point title	Anti-Human Papillomavirus (Anti-HPV)-16/18 antibody titers in serum at years 5, 6 and 7 ^[1]
End point description: Anti-HPV-16/18 antibody titers are presented as Geometric Mean Titers (GMTs) and expressed in enzyme-linked immunosorbent assay (ELISA) units per milliliter (EL.U/mL). The immune response of the HPV-16/18 vaccine (as determined by anti-HPV-16/18 antibodies assessed by ELISA) in the HPV-060 study population was compared with the immune response obtained in study HPV-001 and its long-term follow-up studies HPV-007/HPV-023 at equivalent timepoints and with the immune response obtained after natural infection in subjects from study HPV-008. The immune response data for the efficacy studies HPV-001/HPV-007/HPV-023 can be found under the NCT record NCT00518336. The immune response data for the HPV-008 study can be found under the NCT record NCT00122681.	
End point type	Primary
End point timeframe: At Years 5, 6 and 7	

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 analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	146	146	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 [Year 5] (N=128,127,118)	1495.7 (1249.2 to 1790.9)	518.7 (423.2 to 635.6)	282.4 (234.3 to 340.5)	
Anti-HPV-16 [Year 6] (N=128,130, 116)	1344.6 (1130.2 to 1599.6)	526.0 (434.7 to 636.4)	277.7 (228.0 to 338.2)	

Anti-HPV-16 [Year 7] (N=125, 119, 111)	1014.0 (847.0 to 1214.0)	369.5 (295.7 to 461.7)	201.4 (163.6 to 247.9)	
Anti-HPV-18 [Year 5] (N=134, 144, 146)	440.4 (367.8 to 527.2)	168.8 (140.7 to 202.4)	104.6 (86.0 to 127.2)	
Anti-HPV-18 [Year 6] (N=133, 146, 142)	438.2 (366.6 to 523.7)	167.5 (138.1 to 203.1)	97.6 (79.2 to 120.3)	
Anti-HPV-18 [Year 7] (N=130, 136, 137)	307.8 (256.2 to 369.7)	119.8 (98.4 to 145.9)	81.7 (65.7 to 101.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HPV-16/18 antibody titers in serum at years 8, 9 and 10

End point title	Anti-HPV-16/18 antibody titers in serum at years 8, 9 and 10 ^[2]
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End point description:

Anti-HPV-16/18 antibody titers are presented as Geometric Mean Titers (GMTs) and expressed in EL.U/mL.

The immune response of the HPV-16/18 vaccine (as determined by anti-HPV-16/18 antibodies assessed by ELISA) in the HPV-060 study population was compared with the immune response obtained in study HPV-001 and its long-term follow-up studies HPV-007/HPV-023 at equivalent timepoints and with the immune response obtained after natural infection in subjects from study HPV-008.

The immune response data for the efficacy studies HPV-001/HPV-007/HPV-023 can be found under the NCT number NCT00518336. The immune response data for the HPV-008 study can be found under the NCT number NCT00122681.

End point type	Primary
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End point timeframe:

At Years 8, 9 and 10

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 analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	148	132	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 [Year 8] (N=116, 106, 99)	1123.3 (930.2 to 1356.5)	392.1 (315.3 to 487.7)	189.1 (153.0 to 233.7)	
Anti-HPV-16 [Year 9] (N=127, 132, 110)	980.9 (825.5 to 1165.6)	366.5 (303.5 to 442.6)	180.2 (148.4 to 218.7)	
Anti-HPV-16 [Year 10] (N=123, 121, 107)	965.4 (802.2 to 1161.8)	334.4 (270.5 to 413.5)	157.4 (128.4 to 193.1)	
Anti-HPV-18 [Year 8] (N=120, 123, 120)	375.1 (310.6 to 453.0)	134.1 (107.5 to 167.4)	82.6 (65.9 to 103.6)	
Anti-HPV-18 [Year 9] (N=132, 148, 132)	327.4 (273.4 to 392.1)	122.5 (101.1 to 148.4)	75.6 (60.9 to 94.0)	
Anti-HPV-18 [Year 10] (N=127, 142, 130)	321.1 (265.0 to 389.1)	115.4 (93.9 to 142.0)	69.7 (56.0 to 86.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of seroconverted subjects for anti-HPV-16 and anti-HPV-18 antibodies at years 5, 6 and 7

End point title	Number of seroconverted subjects for anti-HPV-16 and anti-HPV-18 antibodies at years 5, 6 and 7 ^[3]
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End point description:

Seroconversion was defined as the appearance of anti-HPV-16 and anti-HPV-18 antibodies [i.e. antibody titer greater than or equal to (\geq) the cut-off value] in the serum of subjects seronegative before vaccination in the primary study HPV-014 (NCT00196937). Cut-off values were 8 EL.U/mL for anti-HPV-16 antibody titers and 7 EL.U/mL for anti-HPV-18 antibody titers.

End point type	Primary
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End point timeframe:

At Years 5, 6 and 7

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 analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	146	146	
Units: Subjects				
anti-HPV-16 [Year 5] (N=128, 127, 118)	128	127	118	
anti-HPV-16 [Year 6] (N= 128, 130, 116)	128	130	116	
anti-HPV-16 [Year 7] (N=125, 119, 111)	125	119	111	
anti-HPV-18 [Year 5] (N=134, 144, 146)	134	144	143	
anti-HPV-18 [Year 6] (N=133, 146, 142)	133	146	138	
anti-HPV-18 [Year 7] (N=130, 136, 137)	130	135	131	

Statistical analyses

No statistical analyses for this end point

Primary: Number of seroconverted subjects for anti-HPV-16 and anti-HPV-18 antibodies at years 8, 9 and 10

End point title	Number of seroconverted subjects for anti-HPV-16 and anti-HPV-18 antibodies at years 8, 9 and 10 ^[4]
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End point description:

Seroconversion was defined as the appearance of anti-HPV-16 and anti-HPV-18 antibodies (i.e. antibody titer \geq the cut-off value) in the serum of subjects seronegative before vaccination in the primary study HPV-014 (NCT00196937). Cut-off values were 19 EL.U/mL for anti-HPV-16 antibody titers and 18 EL.U/mL for anti-HPV-18 antibody titers.

End point type	Primary
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End point timeframe:

At Years 8, 9 and 10

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 analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	148	132	
Units: Subjects				
anti-HPV-16 [Year 8] (N= 116, 106, 99)	116	106	95	
anti-HPV-16 [Year 9] (N=127, 132, 110)	127	132	106	
anti-HPV-16 [Year 10] (N=123, 121, 107)	123	120	103	
anti-HPV-18 [Year 8] (N=120, 123, 120)	120	118	104	
anti-HPV-18 [Year 9] (N=132, 148, 132)	132	141	113	
anti-HPV-18 [Year 10] (N=127, 142, 130)	126	133	109	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 secretion antibody titers in cervico-vaginal secretion (CVS) samples at Years 5 and 6 in a subset of subjects

End point title	Anti-HPV-16/18 secretion antibody titers in cervico-vaginal secretion (CVS) samples at Years 5 and 6 in a subset of subjects
End point description:	Anti-HPV-16/18 titers in CVS samples are presented as GMTs and expressed in EL.U/mL.
End point type	Secondary
End point timeframe:	At Year 5 and Year 6

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	39	28	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 [Year 5] (N= 39, 39, 28)	90.2 (61.9 to 131.3)	47.2 (32.2 to 69.2)	56.8 (28.7 to 112.4)	
Anti-HPV-18 [Year 5] (N= 39, 39, 28)	30.9 (20.9 to 45.6)	24.6 (14.8 to 41.0)	33.3 (15.8 to 70.0)	

Anti-HPV-16 [Year 6] (N=29, 29, 26)	80.3 (46.8 to 137.8)	43.8 (26.0 to 73.9)	37.1 (20.8 to 66.0)	
Anti-HPV-18 [Year 6] (N= 29, 29, 26)	22.9 (13.8 to 37.9)	19.9 (11.4 to 34.9)	19.2 (11.7 to 31.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 secretion antibody titers in CVS samples at Years 7, 8, 9 and 10 in a subset of subjects

End point title	Anti-HPV-16/18 secretion antibody titers in CVS samples at Years 7, 8, 9 and 10 in a subset of subjects
End point description:	Anti-HPV-16/18 titers in CVS samples are presented as GMTs and expressed in EL.U/mL.
End point type	Secondary
End point timeframe:	At Years 7, 8, 9 and 10

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	40	32	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 [Year 7] (N=31, 30, 30)	63.0 (38.6 to 102.9)	33.3 (21.6 to 51.2)	42.3 (25.0 to 71.5)	
Anti-HPV-18 [Year 7] (N=31, 31, 30)	33.5 (19.8 to 56.6)	17.5 (10.2 to 30.1)	49.0 (22.4 to 107.3)	
Anti-HPV-16 [Year 8] (N=31, 34, 32)	45.6 (29.6 to 70.1)	43.9 (24.8 to 77.7)	54.6 (34.3 to 86.8)	
Anti-HPV-18 [Year 8] (N=31, 34, 32)	17.8 (11.2 to 28.4)	26.2 (14.7 to 46.8)	31.9 (14.7 to 69.2)	
Anti-HPV-16 [Year 9] (N=32, 35, 27)	67.7 (45.4 to 101.0)	42.6 (23.6 to 76.8)	62.6 (36.7 to 106.5)	
Anti-HPV-18 [Year 9] (N=32, 35, 27)	28.1 (18.5 to 42.8)	23.9 (15.8 to 36.1)	50.4 (25.1 to 101.3)	
Anti-HPV-16 [Year 10] (N=41, 40, 26)	43.4 (28.1 to 67.1)	34.3 (24.1 to 48.7)	56.0 (31.5 to 99.7)	
Anti-HPV-18 [Year 10] (N=41, 40, 26)	29.4 (17.6 to 49.4)	22.7 (13.8 to 37.3)	45.1 (22.9 to 88.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total Immunoglobulin G (IgG) secretion antibody titers in CVS samples

at Years 5 and 6 in a subset of subjects

End point title	Total Immunoglobulin G (IgG) secretion antibody titers in CVS samples at Years 5 and 6 in a subset of subjects
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End point description:

IgG antibody titers in CVS samples are presented as GMTs and expressed in microgram per milliliter (µg/mL).

End point type	Secondary
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End point timeframe:

At Year 5 and Year 6

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	39	28	
Units: µg/mL				
geometric mean (confidence interval 95%)				
IgG secretion antibodies [Year 5] (N=39, 39, 28)	577.8 (411.3 to 811.6)	550.5 (373.7 to 811.0)	990.6 (540.2 to 1816.4)	
IgG secretion antibodies [Year 6] (N=29, 29, 26)	546.5 (352.2 to 848.2)	499.8 (327.7 to 762.2)	1012.9 (696.7 to 1472.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total IgG secretion antibody titers in CVS samples at Years 7, 8, 9, and 10 in a subset of subjects

End point title	Total IgG secretion antibody titers in CVS samples at Years 7, 8, 9, and 10 in a subset of subjects
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End point description:

Total IgG antibody titers in CVS samples are presented as GMTs and expressed in microgram per milliliter (µg/mL).

End point type	Secondary
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End point timeframe:

At Years 7, 8, 9 and 10

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	37	32	
Units: µg/mL				
geometric mean (confidence interval 95%)				
IgG secretion antibodies [Year 7] (N=31, 31, 30)	517.5 (348.1 to 769.4)	372.2 (236.7 to 585.4)	1263.2 (793.8 to 2010.2)	

IgG secretion antibodies [Year 8] (N=31, 34, 32)	304.8 (211.1 to 440.1)	457.2 (308.2 to 678.2)	928.2 (578.0 to 1490.6)	
IgG secretion antibodies [Year 9] (N=32, 33, 26)	435.1 (293.2 to 645.8)	460.4 (301.7 to 702.4)	925.8 (586.3 to 1461.8)	
IgG secretion antibodies [Year 10] (N=39, 37, 24)	315.3 (237.9 to 417.8)	373.5 (259.9 to 536.8)	622.9 (405.2 to 957.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total IgG antibody titers in serum at Years 5, 6 and 7 based on the ATP cohort for immunogenicity

End point title	Total IgG antibody titers in serum at Years 5, 6 and 7 based on the ATP cohort for immunogenicity
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End point description:

Total IgG antibody titers are presented as GMTs and expressed in µg/mL.

End point type	Secondary
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End point timeframe:

At Years 5, 6 and 7

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	65	60	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Total IgG serum antibodies [Year 5] (N=68, 65, 60)	19481.8 (18076.2 to 20996.8)	18388.2 (16844.6 to 20073.3)	17657.2 (16046.7 to 19429.4)	
Total IgG serum antibodies [Year 6] (N=41, 38, 33)	13376.5 (12498.7 to 14315.9)	12262.7 (11304.8 to 13301.8)	12040.2 (10854.4 to 13355.7)	
Total IgG serum antibodies [Year 7] (N=59, 63, 57)	13957.2 (13116.6 to 14851.7)	13179.4 (12287.7 to 14135.7)	12992.9 (12096.9 to 13955.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total IgG antibody titers in serum at Years 8, 9 and 10 based on the ATP cohort for immunogenicity

End point title	Total IgG antibody titers in serum at Years 8, 9 and 10 based on the ATP cohort for immunogenicity
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End point description:

Total IgG antibody titers are presented as GMTs and expressed in µg/mL.

End point type	Secondary
End point timeframe:	
At Years 8, 9 and 10	

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	62	55	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Total IgG serum antibodies [Year 8] (N=57, 58, 55)	11059.5 (10547.8 to 11596.0)	10656.3 (10057.6 to 11290.6)	10605.7 (10061.4 to 11179.5)	
Total IgG serum antibodies [Year 9] (N=60, 56, 54)	11212.2 (10661.3 to 11791.6)	10693.8 (10067.0 to 11359.7)	10427.8 (9871.3 to 11015.6)	
Total IgG serum antibodies [Year 10] (N=61,62,51)	11071.3 (10546.9 to 11621.8)	10650.8 (10079.2 to 11254.7)	10535.0 (9979.4 to 11121.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total IgG antibody titers in serum at Years 5, 6 and 7 based on the TVC

End point title	Total IgG antibody titers in serum at Years 5, 6 and 7 based on the TVC
End point description:	
Total IgG antibody titers are presented as GMTs and expressed in µg/mL.	
End point type	Secondary
End point timeframe:	
At Years 5, 6 and 7	

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	68	61	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Total IgG serum antibodies [Year 5] (N=69, 68, 61)	19453.0 (18068.5 to 20943.6)	18092.4 (16566.3 to 19759.1)	17885.0 (16224.1 to 19715.9)	
Total IgG serum antibodies [Year 6] (N=42, 39, 33)	13318.5 (12458.3 to 14238.1)	12173.1 (11231.2 to 13193.9)	12040.2 (10854.4 to 13355.7)	

Total IgG serum antibodies [Year 7] (N=59, 66, 58)	13957.2 (13116.6 to 14851.7)	13059.5 (12205.2 to 13973.6)	13052.9 (12160.9 to 14010.5)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Total IgG antibody titers in serum at Years 8, 9 and 10 based on the TVC

End point title	Total IgG antibody titers in serum at Years 8, 9 and 10 based on the TVC
End point description:	Total IgG antibody titers are presented as GMTs and expressed in µg/mL.
End point type	Secondary
End point timeframe:	At Years 8, 9 and 10

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	66	57	
Units: µg/mL				
geometric mean (confidence interval 95%)				
Total IgG serum antibodies [Year 8] (N=58, 61, 57)	11084.4 (10578.2 to 11614.8)	10602.4 (10010.8 to 11229.1)	10725.5 (10151.1 to 11332.4)	
Total IgG serum antibodies [Year 9] (N=60, 56, 54)	11212.2 (10661.3 to 11791.6)	10693.8 (10067.0 to 11359.7)	10427.8 (9871.3 to 11015.6)	
Total IgG serum antibodies [Year 10] (N=62,66,55)	11043.6 (10526.3 to 11586.4)	10511.3 (9938.6 to 11117.0)	10484.8 (9947.5 to 11051.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 4 in primary study HPV-014 (NCT00196937) to Year 5 in the present study

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 4 in primary study HPV-014 (NCT00196937) to Year 5 in the present study
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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, or may have evolved into one of the outcomes listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
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End point timeframe:

From Year 4 in primary study HPV-014 (NCT00196937) up to Year 5 in present HPV-060 study

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153	184	170	
Units: Subjects				
Fatal SAE(s) (N=153, 184, 170)	0	0	0	
Related SAE(s) (N=153, 184, 170)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 5 to Year 6

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 5 to Year 6
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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, or may have evolved into one of the outcomes listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
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End point timeframe:

From Year 5 up to Year 6

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	177	164	
Units: Subjects				
Fatal SAE(s) (N= 147, 177, 164)	0	0	0	
Related SAE(s) (N= 147, 177, 164)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 6 to Year 7

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 6 to Year 7
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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, or may have evolved into one of the outcomes listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
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End point timeframe:

From Year 6 up to Year 7

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149	165	160	
Units: Subjects				
Fatal SAE(s) (N=149, 165, 160)	0	0	0	
Related SAE(s) (N=149, 165, 160)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 7 to Year 8

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 7 to Year 8
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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, or may have evolved into one of the outcomes

listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
End point timeframe:	
From Year 7 up to Year 8	

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	152	141	
Units: Subjects				
Fatal SAE(s) (N=137, 152, 141)	0	0	0	
Related SAE(s) (N=137, 152, 141)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 8 to Year 9

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 8 to Year 9
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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, or may have evolved into one of the outcomes listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
End point timeframe:	
From Year 8 up to Year 9	

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	146	180	157	
Units: Subjects				
Fatal SAE(s) (N=146, 180, 157)	0	0	1	
Related SAE(s) (N=146, 180, 157)	0	1	0	

Statistical analyses

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 9 to Year 10

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 9 to Year 10
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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, or may have evolved into one of the outcomes listed above. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
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End point timeframe:

From Year 9 up to Year 10

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	172	156	
Units: Subjects				
Fatal SAE(s) (N=142, 172, 156)	0	0	0	
Related SAE(s) (N=142, 172, 156)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 0 to Year 10

End point title	Number of subjects with any fatal or vaccine-related SAEs (including SAEs related to study procedures and GlaxoSmithKline Biologicals' concomitant medication) from Year 0 to Year 10
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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. Related SAE = SAE assessed by the investigator as causally related to the study vaccine administered in study HPV-014 (NCT00196937).

End point type	Secondary
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End point timeframe:

From Year 0 up to Year 10

End point values	Cervarix 15-25 years group	Cervarix 26-45 years group	Cervarix 46-55 years group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	194	171	
Units: Subjects				
Fatal SAE(s) (N=159, 194, 171)	0	1	1	
Related SAE(s) (N=159, 194, 171)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

SAEs: Throughout the entire study period (from Year 0 up to the Year 10).

Adverse event reporting additional description:

Other (non-serious) Adverse Events and solicited symptoms were not collected/assessed. This section displays the safety analysis on the subjects who participated in the primary study HPV-014 (NCT00196937), excluding those who were not selected or not consented for the present study HPV-060 (NCT00947115).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Cervarix 15-25 years group
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Reporting group description:

Women, aged 15 to 25 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

Reporting group title	Cervarix 46-55 years group
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Reporting group description:

Women, aged 46 to 55 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

Reporting group title	Cervarix 26-45 years group
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Reporting group description:

Women, aged 26 to 45 at the time of primary vaccination, who were vaccinated with Cervarix intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule in the primary study HPV-014 (NCT00196937).

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 adverse events were not collected in this study.

Serious adverse events	Cervarix 15-25 years group	Cervarix 46-55 years group	Cervarix 26-45 years group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 159 (0.00%)	1 / 171 (0.58%)	2 / 194 (1.03%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 171 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung neoplasm malignant			

subjects affected / exposed	0 / 159 (0.00%)	1 / 171 (0.58%)	0 / 194 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 171 (0.00%)	1 / 194 (0.52%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cervarix 15-25 years group	Cervarix 46-55 years group	Cervarix 26-45 years group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 159 (0.00%)	0 / 171 (0.00%)	0 / 194 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2013	<ul style="list-style-type: none">• The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18.• The IgG ELISA assay was replaced by IgG nephelometry assay to measure total IgG in the serum matrix because the assay output of nephelometry was proven less variable than that of ELISA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported