Clinical trial results:
A phase IIIb, open, multi-centre gynaecological extension study for follow-up of a subset of 580299/008 study subjects who were either cervical cytology negative and oncogenic HPV positive or pregnant at their final 580299/008 study visit (Visit 10 at Month 48)

Summary

EudraCT number	2008-008124-33
Trial protocol	FI ES DE GB
Global end of trial date	20 January 2014

Results information

Result version number	v2 (current)
This version publication date	02 November 2019
First version publication date	24 January 2015
Version creation reason	• Correction of full data set Results have been amended to account for consistency with other registries.

Trial information

Trial identification

Sponsor protocol code	112024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00937950
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 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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	04 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2014
Global end of trial reached?	Yes
Global end of trial date	20 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To provide clinical management and, if required, treatment to subjects who at the end of the HPV-008 study displayed normal cervical cytology but tested positive for oncogenic HPV infection or to subjects who were pregnant at the end of the HPV-008 study so that no cervical sample could be collected.
- To report fatal serious adverse events (SAEs), SAEs related to study participation and SAEs related to a concurrent GSK medication in all subjects.

Protection of trial subjects:

As with all injectable vaccines, appropriate medical treatment was always readily available in case of anaphylactic reactions following the administration of the vaccine in the HPV-008 (NCT00122681) study. For this reason, the vaccinee remained under medical supervision for 30 minutes after vaccination in the HPV-008 (NCT00122681) study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Finland: 764
Country: Number of subjects enrolled	Germany: 92
Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 211
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Philippines: 308
Country: Number of subjects enrolled	Taiwan: 105
Country: Number of subjects enrolled	Thailand: 249
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	2022
EEA total number of subjects	965

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)	2022
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of the 2022 subjects enrolled in this study, 19 were excluded for reasons of non-eligibility, hence only 2003 started the study.

Pre-assignment period milestones

Number of subjects started	2022
Number of subjects completed	2003

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subjects not eligible: 19

Period 1

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

Arms

Arm title	HPV-052 study subjects Group

Arm description:

The study group consisted of a subset of HPV-008 (NCT00122681) study subjects (15-25 years old at first study vaccination), who at their last study visit (Visit 10, Month 48) in HPV-008 (NCT00122681) study displayed normal cervical cytology, but were tested
positive for oncogenic HPV infection, or were pregnant and hence no cervical sample could be collected at their HPV-008 (NCT00122681) concluding visit.

Arm type	Gynaecological follow-up (safety data collection)
Investigational medicinal product name	Havrix
Investigational medicinal product code	
Other name	Hepatitis A vaccine
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received a gynaecological follow-up with cytology and oncogenic HPV DNA testing every 12 months, for up to four years in this gynaecological follow-up study (HPV-052 EXT 008). No vaccine was administered in this extension study.
Subjects received 3 doses of Havrix vaccine, administered intramuscularly, according to a 0, 1, 6-month vaccination schedule in the HPV-008 (NCT00122681) primary study.

Investigational medicinal product name	Cervarix
Investigational medicinal product code	
Other name	HPV-16/18 L1 VLP AS04
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received a gynaecological follow-up with cytology and oncogenic HPV DNA testing every 12 months, for up to four years in this gynaecological follow-up study (HPV-052 EXT 008). No vaccine was administered in this extension study.
Subjects received 3 doses of Cervarix vaccine, administered intramuscularly, according to a 0, 1, 6-month vaccination schedule in the HPV-008 (NCT00122681) primary study.

Number of subjects in period 1[1]	HPV-052 study subjects Group
Started	2003
Completed	1787
Not completed	216
Consent withdrawn by subject	23
Others	18
Migrated/moved from study area	27
Lost to follow-up	144
Missing confirmed	4

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 2022 subjects enrolled, 19 did not fulfill eligibility criteria and were excluded, hence 2003 subjects started the study.

Baseline characteristics

Reporting groups	
Reporting group title	HPV-052 study subjects Group

Reporting group description:

The study group consisted of a subset of HPV-008 (NCT00122681) study subjects (15-25 years old at first study vaccination), who at their last study visit (Visit 10, Month 48) in HPV-008 (NCT00122681) study displayed normal cervical cytology, but were tested
positive for oncogenic HPV infection, or were pregnant and hence no cervical sample could be collected at their HPV-008 (NCT00122681) concluding visit.

Reporting group values	HPV-052 study subjects Group	Total	
Number of subjects	2003	2003	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2003	2003	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
geometric mean	24.3		
standard deviation	± 3.06	-	
Gender categorical Units: Subjects			
Female	2003	2003	
Male	0	0	
Race Units: Subjects			
Black	58	58	
White/Caucasian	1211	1211	
Arabic/north African	4	4	
East & south east Asian	549	549	
South Asian	3	3	
Hispanic	21	21	
Chinese	106	106	
Indian	1	1	
Not specified	50	50	

End points

End points reporting groups

Reporting group title	HPV-052 study subjects Group

Reporting group description:

The study group consisted of a subset of HPV-008 (NCT00122681) study subjects (15-25 years old at first study vaccination), who at their last study visit (Visit 10, Month 48) in HPV-008 (NCT00122681) study displayed normal cervical cytology, but were tested
positive for oncogenic HPV infection, or were pregnant and hence no cervical sample could be collected at their HPV-008 (NCT00122681) concluding visit.

Primary: Number of subjects with HPV DNA in cervical samples by Hybrid Capture 2 test (HCII)

End point title	Number of subjects with HPV DNA in cervical samples by Hybrid Capture 2 test (HCII)[1]

End point description:

Subjects who presented oncogenic HPV DNA in cervical samples by HPV DNA testing. The presence of oncogenic HPV infection was determined by the Hybrid Capture 2 (HCII) test, which detects HPV DNA types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.
Missing = For some of the subjects whose result was indicated as quantity not sufficient (QNS).

End point type	Primary

End point timeframe:

At Months 12, 24, 36, 48

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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	1467			
Units: Subjects				
Positive DNA (Month 12 Post HPV-008) (N=1467)	615			
Negative DNA (Month 12 Post HPV-008) (N=1467)	828			
Missing DNA (Month 12 Post HPV-008) (N=1467)	24			
Positive DNA (Month 24 Post HPV-008) (N=869)	418			
Negative DNA (Month 24 Post HPV-008) (N=869)	444			
Missing DNA (Month 24 Post HPV-008) (N=869)	7			
Positive DNA (Month 36 Post HPV-008) (N=495)	255			
Negative DNA (Month 36 Post HPV-008) (N=495)	236			
Missing DNA (Month 36 Post HPV-008) (N=495)	4			
Positive DNA (Month 48 Post HPV-008) (N=258)	144			
Negative DNA (Month 48 Post HPV-008) (N=258)	107			

Missing DNA (Month 48 Post HPV-008) (N=258)	7			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with colposcopy referral and colposcopy adequacy

End point title	Number of subjects with colposcopy referral and colposcopy adequacy[2]

End point description:

Subjects with normal cervical cytology, who were found to be oncogenic HPV DNA positive in two subsequent tests, were referred to colposcopy. The result of the subjects' last HPV-008 study visit was taken into account at Visit 1. Subjects with a single cervical cytology reading of ≥ atypical squamous cells of undetermined significance (ASC-US) positive for oncogenic HPV DNA were referred for colposcopy. Subjects with a single cervical cytology reading of ≥ low grade squamous intraepithelial lesion (LSIL) were referred to colposcopy, irrespective of their oncogenic HPV DNA test result.

End point type	Primary

End point timeframe:

At Months 12, 24, 36, 48

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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	2003			
Units: Subjects				
Colposcopy referral (Month 12) Yes (N=2003)	572			
Colposcopy referral (Month 12) No (N=2003)	1429			
Colposcopy referral (Month 12) Missing (N=2003)	2			
Algorithm respected (Month 12) Yes (N=392)	371			
Algorithm respected (Month 12) No (N=392)	21			
Colposcopy adequacy(Month12), Satisfactory(N=392)	370			
Colposcopy adequacy(Month12),Unsatisfactory(N=3	18			
Colposcopy adequacy (Month 12), Missing (N=392)	4			
Colposcopy referral (Month 24) Yes (N=2003)	385			
Colposcopy referral (Month 24) No (N=2003)	1615			
Colposcopy referral (Month 24) Missing (N=2003)	3			
Algorithm respected (Month 24) Yes (N=263)	254			

Algorithm respected (Month 24) No (N=263)	8			
Algorithm respected (Month 24) Missing (N=263)	1			
Colposcopy adequacy(Month24), Satisfactory(N=263)	245			
Colposcopy adequacy(Month24),Unsatisfactory(N=2	14			
Colposcopy adequacy (Month 24), Missing (N=263)	4			
Colposcopy referral (Month 36) Yes (N=2003)	224			
Colposcopy referral (Month 36) No (N=2003)	1776			
Colposcopy referral (Month 36) Missing (N=2003)	3			
Algorithm respected (Month 36) Yes (N=158)	154			
Algorithm respected (Month 36) No (N=158)	4			
Colposcopy adequacy(Month36), Satisfactory(N=158)	150			
Colposcopy adequacy(Month36),Unsatisfactory(N=1	7			
Colposcopy adequacy (Month 36), Missing (N=158)	1			
Colposcopy referral (Month 48) Yes (N=2003)	133			
Colposcopy referral (Month 48) No (N=2003)	1867			
Colposcopy referral (Month 48) Missing (N=2003)	3			
Algorithm respected (Month 48) Yes (N=96)	96			
Algorithm respected (Month 48) No (N=96)	0			
Colposcopy adequacy(Month48), Satisfactory(N=96)	92			
Colposcopy adequacy(Month48),Unsatisfactory(N=9	3			
Colposcopy adequacy (Month 48), Missing (N=96)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with cytological abnormalities in cervical samples by ThinPrep PapTest

End point title	Number of subjects with cytological abnormalities in cervical samples by ThinPrep PapTest[3]

End point description:

Subjects who presented normal, ASC-US (Atypical Squamous Cell of Undetermined Significance), LSIL (Low-grade Squamous Intraepithelial Lesions), HSIL (High-grade Squamous Intraepithelial Lesions), AGC (Atypical Glandular Cells), ASC-H (Atypical Squamous Cells cannot exclude HSIL) cervical cytology. Cervical cytology examination was performed using the ThinPrep PapTest.
Note: One subject may have presented with different cytology results at the yearly visit throughout the maximum 4-year follow-up period and therefore may be counted in more than one result category in the

analysis.

End point type	Primary

End point timeframe:

At Months 12, 24, 36, 48

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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	1467			
Units: Subjects				
Normal, Month 12 (N=1467)	1193			
ASC-US, Month 12 (N=1467)	154			
ASC-H, Month 12 (N=1467)	8			
LSIL, Month 12 (N=1467)	100			
HSIL, Month 12 (N=1467)	8			
AGC, Month 12 (N=1467)	4			
Normal, Month 24 (N=867)	662			
ASC-US, Month 24 (N=867)	117			
ASC-H, Month 24 (N=867)	11			
LSIL, Month 24 (N=867)	68			
HSIL, Month 24 (N=867)	7			
AGC, Month 24 (N=867)	2			
Normal, Month 36 (N=494)	390			
ASC-US, Month 36 (N=494)	58			
ASC-H, Month 36 (N=494)	4			
LSIL, Month 36 (N=494)	34			
HSIL, Month 36 (N=494)	5			
AGC, Month 36 (N=494)	3			
Normal, Month 48 (N=258)	206			
ASC-US, Month 48 (N=258)	28			
ASC-H, Month 48 (N=258)	0			
LSIL, Month 48 (N=258)	16			
HSIL, Month 48 (N=258)	6			
AGC, Month 48 (N=258)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with cervical biopsy results at Month 12

End point title	Number of subjects with cervical biopsy results at Month 12[4]

End point description:

Subjects with negative and positive cervical biopsy results for only CIN1, only CIN2, only CIN3, CIN1 and CIN2, CIN1 and CIN3, CIN2 and CIN3, CIN1 and CIN2 and CIN3, AIS, Invasive malignancy, other. CIN = Cervical intraepithelial neoplasia. CIN1/CIN2/CIN3 = Cervical intraepithelial neoplasia grade 1/grade 2/grade 3.

Note: Only CIN1/Only CIN2/Only CIN3 categories contain the subject who has only CIN1/CIN2/CIN3, but not the combinations.

End point type	Primary

End point timeframe:

At Month 12

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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	199			
Units: Subjects				
Negative	76			
Only CIN1(positive)	41			
Only CIN1(negative)	158			
Only CIN2 (positive)	18			
Only CIN2 (negative)	181			
Only CIN3 (positive)	8			
Only CIN3 (negative)	191			
CIN1 and CIN2 (positive)	3			
CIN1 and CIN2(negative)	196			
CIN1 and CIN3(positive)	1			
CIN1 and CIN3 (negative)	198			
CIN2 and CIN3 (positive)	1			
CIN2 and CIN3 (negative)	198			
CIN1 and CIN2 and CIN3 (positive)	0			
CIN1 and CIN2 and CIN3 (negative)	199			
AIS (positive)	0			
AIS (negative)	199			
Invasive malignancy (positive)	0			
Invasive malignancy (negative)	199			
Other	85			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with cervical biopsy results at Month 24

End point title	Number of subjects with cervical biopsy results at Month 24[5]

End point description:

Subjects with negative and positive cervical biopsy results for only CIN1, only CIN2, only CIN3, CIN1 and CIN2, CIN1 and CIN3, CIN2 and CIN3, CIN1 and CIN2 and CIN3, AIS, Invasive malignancy, other. CIN = Cervical intraepithelial neoplasia. CIN1/CIN2/CIN3 = Cervical intraepithelial neoplasia grade 1/grade 2/grade 3.
Note: Only CIN1/Only CIN2/Only CIN3 categories contain the subject who has only CIN1/CIN2/CIN3, but not the combinations.

End point type	Primary

End point timeframe:

At Month 24

Notes:

[5] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	147			
Units: Subjects				
Negative	38			
Only CIN1(positive)	47			
Only CIN1(negative)	100			
Only CIN2 (positive)	8			
Only CIN2 (negative)	139			
Only CIN3 (positive)	8			
Only CIN3 (negative)	139			
CIN1 and CIN2 (positive)	2			
CIN1 and CIN2(negative)	145			
CIN1 and CIN3(positive)	0			
CIN1 and CIN3 (negative)	147			
CIN2 and CIN3 (positive)	1			
CIN2 and CIN3 (negative)	146			
CIN1 and CIN2 and CIN3 (positive)	0			
CIN1 and CIN2 and CIN3 (negative)	147			
AIS (positive)	1			
AIS (negative)	146			
Invasive malignancy (positive)	0			
Invasive malignancy (negative)	147			
Other	56			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with cervical biopsy results at Month 36

End point title	Number of subjects with cervical biopsy results at Month 36[6]

End point description:

Subjects with negative and positive cervical biopsy results for only CIN1, only CIN2, only CIN3, CIN1 and CIN2, CIN1 and CIN3, CIN2 and CIN3, CIN1 and CIN2 and CIN3, AIS, Invasive malignancy, other.
CIN = Cervical intraepithelial neoplasia. CIN1/CIN2/CIN3 = Cervical intraepithelial neoplasia grade 1/grade 2/grade 3.
Note: Only CIN1/Only CIN2/Only CIN3 categories contain the subject who has only CIN1/CIN2/CIN3, but not the combinations.

End point type	Primary

End point timeframe:

At Month 36

Notes:

[6] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Subjects				
Negative	31			
Only CIN1(positive)	31			
Only CIN1(negative)	57			
Only CIN2 (positive)	6			
Only CIN2 (negative)	82			
Only CIN3 (positive)	3			
Only CIN3 (negative)	85			
CIN1 and CIN2 (positive)	0			
CIN1 and CIN2(negative)	88			
CIN1 and CIN3(positive)	0			
CIN1 and CIN3 (negative)	88			
CIN2 and CIN3 (positive)	0			
CIN2 and CIN3 (negative)	88			
CIN1 and CIN2 and CIN3 (positive)	0			
CIN1 and CIN2 and CIN3 (negative)	88			
AIS (positive)	0			
AIS (negative)	88			
Invasive malignancy (positive)	0			
Invasive malignancy (negative)	88			
Other	25			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with cervical biopsy results at Month 48

End point title	Number of subjects with cervical biopsy results at Month 48[7]

End point description:

Subjects with negative and positive cervical biopsy results for only CIN1, only CIN2, only CIN3, CIN1 and CIN2, CIN1 and CIN3, CIN2 and CIN3, CIN1 and CIN2 and CIN3, AIS, Invasive malignancy, other. CIN = Cervical intraepithelial neoplasia. CIN1/CIN2/CIN3 = Cervical intraepithelial neoplasia grade 1/grade 2/grade 3.
Note: Only CIN1/Only CIN2/Only CIN3 categories contain the subject who has only CIN1/CIN2/CIN3, but not the combinations.

End point type	Primary

End point timeframe:

At Month 48

Notes:

[7] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Subjects				
Negative	21			
Only CIN1(positive)	15			
Only CIN1(negative)	39			
Only CIN2 (positive)	5			
Only CIN2 (negative)	49			
Only CIN3 (positive)	2			
Only CIN3 (negative)	52			
CIN1 and CIN2 (positive)	1			
CIN1 and CIN2(negative)	53			
CIN1 and CIN3(positive)	0			
CIN1 and CIN3 (negative)	54			
CIN2 and CIN3 (positive)	0			
CIN2 and CIN3 (negative)	54			
CIN1 and CIN2 and CIN3 (positive)	0			
CIN1 and CIN2 and CIN3 (negative)	54			
AIS (positive)	0			
AIS (negative)	54			
Invasive malignancy (positive)	0			
Invasive malignancy (negative)	54			
Other	11			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment referrals by treatment type at Month 12

End point title	Number of subjects with treatment referrals by treatment type at Month 12[8]

End point description:

If a high-grade lesion was detected, the subject was to be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions was to be handled according to local medical practice within the local health care system. The subject's participation in the study concluded after treatment.
The treatment types included the following: Loop excision of cervix, Loop cone of cervix, Cold knife cone of cervix, Laser excision, other.

End point type	Primary

End point timeframe:

At Month 12

Notes:

[8] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	392			
Units: Subjects				
Treatment referral, Yes (N=392)	33			
Treatment referral, No (N=392)	359			
Loop excision of cervix, Yes (N=32)	14			
Loop excision of cervix, No (N=32)	18			
Loop cone of cervix, Yes (N=32)	15			
Loop cone of cervix, No (N=32)	17			
Cold knife cone of cervix, Yes (N=32)	0			
Cold knife cone of cervix, No (N=32)	32			
Laser excision, Yes (N=32)	1			
Laser excision, No (N=32)	31			
Other (N=32)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment referrals by treatment type at Month 24

End point title	Number of subjects with treatment referrals by treatment type at Month 24[9]

End point description:

If a high-grade lesion was detected, the subject was to be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions was to be handled according to local medical practice within the local health care system. The subject's participation in the study concluded after treatment.
The treatment types included the following: Loop excision of cervix, Loop cone of cervix, Cold knife cone of cervix, Laser excision, other.

End point type	Primary

End point timeframe:

At Month 24

Notes:

[9] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	263			
Units: Subjects				
Treatment referral, Yes (N=263)	19			
Treatment referral, No (N=263)	243			
Treatment referral, Missing (N=263)	1			
Loop excision of cervix, Yes (N=17)	9			
Loop excision of cervix, No (N=17)	8			
Loop cone of cervix, Yes (N=17)	4			
Loop cone of cervix, No (N=17)	13			

Cold knife cone of cervix, Yes (N=17)	1			
Cold knife cone of cervix, No (N=17)	16			
Laser excision, Yes (N=17)	0			
Laser excision, No (N=17)	17			
Other (N=17)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment referrals by treatment type at Month 36

End point title	Number of subjects with treatment referrals by treatment type at Month 36[10]

End point description:

If a high-grade lesion was detected, the subject was to be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions was to be handled according to local medical practice within the local health care system. The subject's participation in the study concluded after treatment.
The treatment types included the following: Loop excision of cervix, Loop cone of cervix, Cold knife cone of cervix, Laser excision, other.

End point type	Primary

End point timeframe:

At Month 36

Notes:

[10] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: Subjects				
Treatment referral, Yes (N=158)	13			
Treatment referral, No (N=158)	145			
Loop excision of cervix, Yes (N=10)	4			
Loop excision of cervix, No (N=10)	6			
Loop cone of cervix, Yes (N=10)	4			
Loop cone of cervix, No (N=10)	6			
Cold knife cone of cervix, Yes (N=10)	0			
Cold knife cone of cervix, No (N=10)	10			
Laser excision, Yes (N=10)	0			
Laser excision, No (N=10)	10			
Other (N=10)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with treatment referrals by treatment type at Month 48

End point title	Number of subjects with treatment referrals by treatment type at Month 48[11]

End point description:

If a high-grade lesion was detected, the subject was to be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions was to be handled according to local medical practice within the local health care system. The subject's participation in the study concluded after treatment.
The treatment types included the following: Loop excision of cervix, Loop cone of cervix, Cold knife cone of cervix, Laser excision, other.

End point type	Primary

End point timeframe:

At Month 48

Notes:

[11] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Subjects				
Treatment referral, Yes (N=96)	9			
Treatment referral, No (N=96)	87			
Loop excision of cervix, Yes (N=8)	1			
Loop excision of cervix, No (N=8)	7			
Loop cone of cervix, Yes (N=8)	5			
Loop cone of cervix, No (N=8)	3			
Cold knife cone of cervix, Yes (N=8)	0			
Cold knife cone of cervix, No (N=8)	8			
Laser excision, Yes (N=8)	1			
Laser excision, No (N=8)	7			
Other (N=8)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with adverse events (AEs) or serious adverse events (SAEs) leading to withdrawal

End point title	Number of subjects with adverse events (AEs) or serious adverse events (SAEs) leading to withdrawal[12]

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and 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 vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related

to the vaccination.

End point type	Primary

End point timeframe:

From Month 12 [i.e. 12 months after the last visit in HPV-008 (NCT00122681) primary study) up to Month 48 [i.e. 48 months after the last visit in HPV-008 (NCT00122681) primary study]

Notes:

[12] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	2003			
Units: Subjects	216			

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with any fatal SAEs, with any SAEs assessed as possibly related to study participation or to a concurrent GSK medication

End point title	Number of subjects with any fatal SAEs, with any SAEs assessed as possibly related to study participation or to a concurrent GSK medication[13]

End point description:

SAEs assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity.

End point type	Primary

End point timeframe:

From Month 12 [i.e. 12 months after the last visit in HPV-008 (NCT00122681) primary study) up to Month 48 [i.e. 48 months after the last visit in HPV-008 (NCT00122681) primary study]

Notes:

[13] - 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	HPV-052 study subjects Group			
Subject group type	Reporting group			
Number of subjects analysed	2003			
Units: Subjects				
Subjects with fatal SAEs	0			
Subjects with any related SAEs	0			
Subjects with any SAEs due to concurrent GSK medic	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs and SAEs: From Month 12 [i.e. 12 months after the last visit in HPV-008 (NCT00122681) primary study) up to Month 48 [i.e. 48 months after the last visit in HPV-008 (NCT00122681) primary study].

Adverse event reporting additional description:

Non-serious AEs were not collected in this study. Only fatal SAEs, SAEs related to study participation, SAEs related to a concurrent GSK medication and AEs and SAEs leading to withdrawal from the study were collected in this study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

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

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 AEs were not collected in this study.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported