Clinical trial results:
A Phase IIIb observer-blind, randomized, multicentre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine and Merck's Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine, when administered intramuscularly according to alternative 2-dose schedules in 9-14 year-old healthy females.

Summary

EudraCT number	2011-002035-26
Trial protocol	FR SE
Global end of trial date	27 October 2015

Results information

Result version number	v2
This version publication date	11 November 2016
First version publication date	21 April 2016
Version creation reason	• New data added to full data set Data for M24 and M36 have been added.

Trial information

Trial identification

Sponsor protocol code	115411

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462357
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	01 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2015
Global end of trial reached?	Yes
Global end of trial date	27 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate sequentially if the immunogenicity (as determined by enzyme-linked immunosorbent assay - ELISA) of GSK Biologicals' HPV-16/18 L1 Virus-like-particle (VLP) AS04 vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior/superior to that of Merck's HPV-6/11/16/18 L1 VLP recombinant vaccine administered according to a 2-dose schedule at 0, 6 months in 9-14 year-old females, 1 month after the last dose (Month 7).

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 30 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 72
Country: Number of subjects enrolled	France: 231
Country: Number of subjects enrolled	Hong Kong: 534
Country: Number of subjects enrolled	Singapore: 242
Worldwide total number of subjects	1079
EEA total number of subjects	303

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	539
Adolescents (12-17 years)	540
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1079 subjects entered this study, of which 4 subjects signed an informed consent but did not receive a single dose of the vaccine and were hence not counted as starting the study.

Pre-assignment period milestones

Number of subjects started	1079
Number of subjects completed	1075

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No vaccine administered: 4

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Data was collected in an observer-blind manner. By observer-blind, it is meant that during the course of the study, the vaccine recipient and those responsible for the evaluation of any study endpoint (e.g. immunogenicity, reactogenicity, and safety) were all unaware of which vaccine was administered. To do so, vaccine preparation and administration were be done by authorised medical personnel who did not participate in any of the study clinical evaluation assays.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cervarix 2 dose Group

Arm description:

Subjects who received 2 doses of Cervarix™ vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	HPV 1
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 2 doses of Cervarix™ Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects received 1 dose of 0.5 mL supplied as a liquid in individual pre-filled syringes, administered

intramuscularly in the deltoid muscle of the non-dominant arm at Month 2 to maintain blinding.

Arm title	Gardasil 2 dose Group
Arm description:	
Subjects who received 2 doses of Gardasil® vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Arm type	Experimental
Investigational medicinal product name	Gardasil®
Investigational medicinal product code	
Other name	HPV 2
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Subjects received 2 doses of Gardasil® vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Subjects received 1 dose of 0.5 mL supplied as a liquid in individual pre-filled syringes, administered intramuscularly in the deltoid muscle of the non-dominant arm at Month 2 to maintain blinding.	
Arm title	Gardasil 3 dose Group
Arm description:	
Subjects who received 3 doses of Gardasil® vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Arm type	Experimental
Investigational medicinal product name	Gardasil®
Investigational medicinal product code	
Other name	HPV 2
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use
Dosage and administration details:	
Subjects received 3 doses of Gardasil® vaccine at Day 0, Month 2 and Month 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	

Number of subjects in period 1[1]	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group
Started	359	358	358
Completed at Month 7	358	353	352
Completed at Month 12	356	348	350
Completed at Month 18	356	347	349
Completed at Month 24	355	344	349

Completed at Month 36	351	339	346
Completed	351	339	346
Not completed	8	19	12
Consent withdrawn by subject	3	11	3
Lost to follow-up (incomplete vaccination course)	-	-	2
Death	-	-	1
Lost to follow-up (complete vaccination course)	3	5	5
Migrated/moved from study area	2	3	1

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: 1079 subjects entered this study, of which 4 subjects signed an informed consent but did not receive a single dose of the vaccine and were hence not counted as starting the study.

Baseline characteristics

Reporting groups	
Reporting group title	Cervarix 2 dose Group
Reporting group description:	
Subjects who received 2 doses of Cervarix™ vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Reporting group title	Gardasil 2 dose Group
Reporting group description:	
Subjects who received 2 doses of Gardasil® vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Reporting group title	Gardasil 3 dose Group
Reporting group description:	
Subjects who received 3 doses of Gardasil® vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	

Reporting group values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group
Number of subjects	359	358	358
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	11.5	11.5	11.6
standard deviation	± 1.64	± 1.56	± 1.64
Gender categorical Units: Subjects			
Female	359	358	358
Male	0	0	0

Reporting group values	Total		
Number of subjects	1075		
Age categorical 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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	1075		
Male	0		

End points

End points reporting groups

Reporting group title	Cervarix 2 dose Group
Reporting group description:	
Subjects who received 2 doses of Cervarix™ vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Reporting group title	Gardasil 2 dose Group
Reporting group description:	
Subjects who received 2 doses of Gardasil® vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	
Reporting group title	Gardasil 3 dose Group
Reporting group description:	
Subjects who received 3 doses of Gardasil® vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.	

Primary: Number of seroconverted subjects for Anti-HPV-16/18, as assessed by the enzyme-immunosorbent assay (ELISA)

End point title	Number of seroconverted subjects for Anti-HPV-16/18, as assessed by the enzyme-immunosorbent assay (ELISA)
End point description:	
Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers respectively greater than or equal to 19 and 18 EL.U/mL) in the serum of subjects seronegative before vaccination in the primary study.	
End point type	Primary
End point timeframe:	
One month after the last dose of study vaccine (Month 7)	

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	334	334	
Units: Subjects				
Anti-HPV-16 (N=337,334,334)	337	334	334	
Anti-HPV-18 (N=337,334,334)	337	334	334	

Statistical analyses

Statistical analysis title	Immune response to anti-HPV-16 in terms of SCR
Statistical analysis description:	
To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil® vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).	

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in SCR
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	1.15

Notes:

[1] - Non-inferiority with respect to seroconversion will be shown if, at Months 12, 18, 24 and 36, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the difference (Gardasil 2 dose Group - Cervarix 2 dose Group) is below 5%.

Statistical analysis title	Immune response to anti-HPV-18 in terms of SCR

Statistical analysis description:

To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil® vaccine administered according to a 2- dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in SCR
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	1.14

Notes:

[2] - Non-inferiority with respect to seroconversion will be shown if, at Months 12, 18, 24 and 36, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the difference (Gardasil 2 dose Group - Cervarix 2 dose Group) is below 5%.

Primary: Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point title	Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point description:

Anti-HPV 16/18 antibody concentrations were presented as geometric mean concentrations (GMC) and expressed in ELISA units per milliliter (EL.U/mL) based on ELISA.

End point type	Primary

End point timeframe:

One month after the last dose of study vaccine (Month 7)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	334	334	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 (N=337,334,334)	8311.4 (7745.8 to 8918.3)	5061 (4604.1 to 5563.3)	4864 (4481.9 to 5278.7)	
Anti-HPV-18 (N=337,334,334)	5249.7 (4835.4 to 5699.5)	1213 (1098.7 to 1339.1)	1654.5 (1485.8 to 1842.4)	

Statistical analyses

Statistical analysis title	Immune response to anti-HPV-16 in terms of GMT

Statistical analysis description:

To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil® vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.69

Notes:

[3] - Non-inferiority with respect to GMT will be shown if, at Months 12, 18, 24 and 36, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the GMT ratio (Gardasil 2 dose Group/Cervarix 2 dose Group) is below 2.

Statistical analysis title	Immune response to anti-HPV-18 in terms of GMT

Statistical analysis description:

To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is non-inferior to that of Gardasil® vaccine administered according to a 2- dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	0.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.26

Notes:

[4] - Non-inferiority with respect to GMT will be shown if, at Months 12, 18, 24 and 36, for both anti-HPV-16 and anti-HPV-18 antibodies, the upper limit of the 95% confidence interval (CI) for the GMT ratio (Gardasil 2 dose Group/Cervarix 2 dose Group) is below 2.

Statistical analysis title	Anti-HPV-18 immune response

Statistical analysis description:

To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is superior to that of Gardasil® vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority[5]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	4.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.97
upper limit	5.13

Notes:

[5] - Superiority will be shown if the lower limit of the 95% confidence interval (CI) for the ratio of geometric mean titers (GMTs) (Cervarix 2 dose Group divided by Gardasil 2 dose Group) is above 1 for anti-HPV-18 antibodies with the associated p-value.

Statistical analysis title	Anti-HPV-16 immune response

Statistical analysis description:

To evaluate sequentially if the immunogenicity (as determined by ELISA) of Cervarix™ vaccine administered according to a 2-dose schedule at 0, 6 months is superior to that of Gardasil® vaccine administered according to a 2-dose schedule at 0, 6 months, in 9-14 year-old females, 1 month after the last dose (Month 7).

Comparison groups	Cervarix 2 dose Group v Gardasil 2 dose Group
Number of subjects included in analysis	671
Analysis specification	Pre-specified
Analysis type	superiority[6]
Method	ANOVA
Parameter estimate	GMT ratio
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.49
upper limit	1.91

Notes:

[6] - Superiority will be shown if the lower limit of the 95% confidence interval (CI) for the ratio of geometric mean titers (GMTs) (Cervarix 2 dose Group divided by Gardasil 2 dose Group) is above 1 for anti-HPV-16 antibodies with the associated p-value.

Primary: Anti-HPV-16/18 seroconversion rates assessed by ELISA

End point title	Anti-HPV-16/18 seroconversion rates assessed by ELISA[7]

End point description:

Seroconversion was defined as the appearance of antibodies [i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to 3.1 and 3.2 international units per milliliter (IU/mL), respectively], in the serum of subjects who were seronegative before vaccination in the primary study. The assay cut-offs used for analyses at Month 36 were modified to 3.1 and 3.2 IU/mL, after applying the conversion factor from EL.U/mL to IU/mL.

End point type	Primary

End point timeframe:

At Month 36

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 scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	313	321	
Units: Subjects				
Anti-HPV-16, Month 36 (N=324,313,321)	324	310	320	
Anti-HPV-18, Month 36 (N=324,313,321)	324	270	298	

Statistical analyses

No statistical analyses for this end point

Primary: Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point title	Anti-HPV-16/18 antibody concentrations assessed by ELISA[8]

End point description:

Anti-HPV 16/18 antibody concentrations were presented as geometric mean titers (GMT) and expressed in IU/mL.
Assay cut-offs used for analyses at Month 36 were modified to 3.1 and 3.2 IU/mL respectively, after applying the conversion factor from EL.U/mL to IU/mL.

End point type	Primary

End point timeframe:

At Month 36

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 scope of this primary end point was descriptive, no statistical hypothesis test was performed.

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	313	321	
Units: IU/mL				
geometric mean (confidence interval 95%)				

Anti-HPV-16, Month 36 (N=324,313,321)	175.2 (160.6 to 191.2)	61.6 (54.1 to 70.1)	77.8 (70.2 to 86.3)	
Anti-HPV-18, Month 36 (N=324,313,321)	85.5 (77 to 95)	12.5 (11 to 14.3)	21.1 (18.3 to 24.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates assessed by ELISA

End point title	Anti-HPV-16/18 seroconversion rates assessed by ELISA

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to 19 and 18 EL.U/mL, respectively) in the serum of subjects seronegative before vaccination in the primary study.

End point type	Secondary

End point timeframe:

At Day 0 and Months 12, 18 and 24

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	334	334	
Units: Subjects				
Anti-HPV-16, Day 0 (N=337,334,334)	7	7	12	
Anti-HPV-18, Day 0 (N=337,334,334)	3	3	1	
Anti-HPV-16, Month 12 (N=331,325,327)	330	325	327	
Anti-HPV-18, Month 12 (N=331,325,327)	330	324	327	
Anti-HPV-16, Month 18 (N=329,327,330)	329	326	330	
Anti-HPV-18, Month 18 (N=329,327,330)	329	310	322	
Anti-HPV-16, Month 24 (N=324,320,324)	324	319	324	
Anti-HPV-18, Month 24 (N=324,320,324)	324	298	313	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point title	Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point description:

Anti-HPV 16/18 antibody concentrations were presented as geometric mean concentrations (GMC) and expressed in ELISA units per milliliter (EL.U/mL) based on ELISA.

End point type	Secondary

End point timeframe:

At Day 0 and Months 12, 18 and 24

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	337	334	334	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Day 0 (N=337,334,334)	9.8 (9.5 to 10.2)	9.8 (9.5 to 10.1)	10 (9.7 to 10.3)	
Anti-HPV-18, Day 0 (N=337,334,334)	9.1 (9 to 9.2)	9.1 (9 to 9.2)	9 (9 to 9.1)	
Anti-HPV-16, Month 12 (N=331,325,327)	2247.9 (2052.2 to 2462.2)	1283.9 (1152.1 to 1430.8)	1610.5 (1468.9 to 1765.8)	
Anti-HPV-18, Month 12 (N=331,325,327)	1311.4 (1187.3 to 1448.4)	266 (236.2 to 299.4)	477.8 (422.7 to 540.1)	
Anti-HPV-16, Month 18 (N=329,327,330)	1516.2 (1393.4 to 1649.8)	675.8 (600 to 761.1)	828 (749.8 to 914.4)	
Anti-HPV-18, Month 18 (N=329,327,330)	763.1 (691.3 to 842.5)	133.8 (117.6 to 152.1)	230.8 (202.1 to 263.6)	
Anti-HPV-16, Month 24 (N=324,320,324)	1317.5 (1213.9 to 1430)	514.4 (456.9 to 579.2)	639.9 (579.6 to 706.6)	
Anti-HPV-18, Month 24 (N=324,317,324)	628.6 (569.4 to 694)	107.8 (94.8 to 122.6)	182.2 (159.6 to 208)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates assessed by pseudovirion-based neutralization assay (PBNA) in a subset of subjects

End point title	Anti-HPV-16/18 seroconversion rates assessed by pseudovirion-based neutralization assay (PBNA) in a subset of subjects

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to ≥ 40 ED50) in the serum of subjects seronegative before vaccination in the primary study.
The analysis was based on the According-to-Protocol (ATP) cohort for immunogenicity, which included all evaluable subjects for whom immunogenicity data were available at the time of the analysis.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12 and 18

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	95	93	
Units: Subjects				
Anti-HPV-16, Day 0 (N=92,95,93)	0	1	0	
Anti-HPV-18, Day 0 (N=92,95,93)	0	0	0	
Anti-HPV-16, Month 7 (N=92,95,93)	92	95	93	
Anti-HPV-18, Month 7 (N=92,95,93)	92	95	93	
Anti-HPV-16, Month 12 (N=90,93,91)	90	93	91	
Anti-HPV-18, Month 12 (N=90,93,91)	90	91	91	
Anti-HPV-16, Month 18 (N=90,92,91)	90	89	90	
Anti-HPV-18, Month 18 (N=89,92,92)	89	81	90	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point title	Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point description:

Anti-HPV 16/18 antibody titers were presented as geometric mean titers (GMTs) and expressed in titers using the PBNA.
The analysis was based on the ATP cohort for immunogenicity, which included all evaluable subjects for whom immunogenicity data were available at the time of the analysis.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12 and 18

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92	95	93	
Units: Titer				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Day 0 (N=92,95,93	20 (20 to 20)	20.2 (19.8 to 20.5)	20 (20 to 20)	
Anti-HPV-18, Day 0 (N=92,95,93)	20 (20 to 20)	20 (20 to 20)	20 (20 to 20)	
Anti-HPV-16, Month 7 (N=92,95,93)	51043.8 (42657.9 to 61078.3)	19119.4 (15249 to 23972.1)	21377.9 (16900.1 to 27042.2)	

Anti-HPV-18, Month 7 (N=92,95,93)	23228 (18677 to 28887.8)	4709.9 (3604.2 to 6154.9)	8009.4 (6111.1 to 10497.4)	
Anti-HPV-16, Month 12 (N=90,93,91)	10635.3 (8555.9 to 13220)	3959.4 (3039.1 to 5158.4)	5858.1 (4610.9 to 7442.8)	
Anti-HPV-18, Month 12 (N=90,93,91)	3651.5 (2903.6 to 4592.1)	656.3 (493.6 to 872.6)	1734.2 (1268.4 to 2371)	
Anti-HPV-16, Month 18 (N=90,92,91)	8388.4 (6647.7 to 10584.9)	1953.5 (1386.6 to 2752.3)	2988.9 (2227.2 to 4011.2)	
Anti-HPV-18, Month 18 (N=89,92,92)	2381.1 (1858.7 to 3050.2)	283.1 (209.4 to 382.7)	805.7 (574.4 to 1130.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T-cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD4+ All doubles, Anti-HPV-16, Day 0 (N=57,47,55)	14 (1 to 97)	22 (1 to 73)	33 (1 to 80)	
CD4+ All doubles, Anti-HPV-18, Day 0 (N=57,46,56)	20 (1 to 83)	19 (1 to 101)	24 (1 to 91.5)	
CD4+ All doubles, Anti-HPV-16, Month 7(N=68,63,65)	1604.5 (634.5 to 3253.5)	853 (429 to 1324)	1131 (694 to 1969)	
CD4+ All doubles, Anti-HPV-18, Month 7(N=67,63,66)	897 (522 to 2497)	459 (240 to 761)	654.5 (384 to 1284)	
CD4+ All doubles, Anti-HPV-16, Month12(N=71,66,70)	1121 (659 to 2340)	622.5 (316 to 1261)	844.5 (546 to 1652)	
CD4+ All doubles, Anti-HPV-18, Month12(N=71,68,70)	789 (400 to 1492)	355 (209 to 673.5)	465.5 (205 to 901)	
CD4-d-CD40L, Anti-HPV-16,Day 0 (N=57,47,55)	10 (1 to 78)	14 (1 to 73)	30 (1 to 80)	
CD4-d-CD40L, Anti-HPV-18,Day 0 (N=57,46,56)	14 (1 to 83)	27 (1 to 101)	25.5 (1 to 68.5)	
CD4-d-CD40L, Anti-HPV-16,Month 7(N=68,63.65)	1507.5 (631.5 to 3043)	779 (426 to 1219)	1054 (670 to 1938)	

CD4-d-CD40L, Anti-HPV-18,Month7 (N=67,63,66)	866 (509 to 2379)	418 (227 to 775)	616.5 (344 to 1193)	
CD4-d-CD40L, Anti-HPV-16,Month 12(N=71,66,70)	990 (594 to 2236)	592.5 (280 to 1135)	805 (469 to 1545)	
CD4-d-CD40L, Anti-HPV-18,Month 12(N=71,68,70)	688 (346 to 1435)	340.5 (168 to 604.5)	404 (219 to 737)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD4-d- IFNγ, Anti-HPV-16,Day 0 (N=57,47,55)	1 (1 to 30)	14 (1 to 42)	1 (1 to 28)	
CD4-d- IFNγ, Anti-HPV-18,Day 0(N=57,46,56)	14 (1 to 32)	7 (1 to 35)	1.5 (1 to 31.5)	
CD4-d- IFNγ, Anti-HPV-16,Month 7(N=68,63,65)	351 (164.5 to 829)	314 (141 to 602)	398 (193 to 708)	
CD4-d- IFNγ, Anti-HPV-18,Month 7(N=67,63,66)	218 (108 to 631)	127 (70 to 247)	181.5 (70 to 371)	
CD4-d- IFNγ, Anti-HPV-16,Month 12(N=71,66,70)	326 (110 to 688)	241.5 (86 to 606)	337 (135 to 734)	
CD4-d- IFNγ, Anti-HPV-18,Month 12(N=71,68,70)	174 (87 to 444)	114 (56.5 to 259.5)	155.5 (56 to 315)	
CD4-d-IL-2, Anti-HPV-16,Day 0 (N=57,47,55)	16 (1 to 71)	24 (1 to 68)	33 (1 to 58)	
CD4-d-IL-2, Anti-HPV-18, Day 0 (N=57,46,56)	1 (1 to 42)	30 (1 to 66)	20 (1 to 58)	
CD4-d-IL-2, Anti-HPV-16,Month 7(N=68,63,65)	1323 (537 to 2702.5)	710 (368 to 1058)	875 (580 to 1431)	
CD4-d-IL-2, Anti-HPV-18,Month 7(N=67,63,66)	737 (420 to 2185)	321 (206 to 573)	503 (295 to 869)	
CD4-d-IL-2, Anti-HPV-16,Month 12(N=71,66,70)	922 (528 to 2050)	487.5 (285 to 991)	702.5 (450 to 1379)	
CD4-d-IL-2, Anti-HPV-18,Month 12(N=71,68,70)	620 (311 to 1157)	274 (164.5 to 550.5)	380 (160 to 705)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD4-d-TNFα, Anti-HPV-16,Day 0 (N=57,47,55)	6 (1 to 52)	32 (1 to 73)	16 (1 to 71)	
CD4-d-TNFα, Anti-HPV-18,Day 0 (N=57,46,56)	24 (1 to 73)	19 (1 to 82)	21 (1 to 57)	
CD4-d-TNFα, Anti-HPV-16,Month 7(N=68,63,65)	1103 (432 to 2399)	605 (276 to 919)	804 (458 to 1512)	
CD4-d-TNFα, Anti-HPV-18,Month 7(N=67,63,66)	647 (371 to 1765)	319 (153 to 594)	517 (272 to 978)	
CD4-d-TNFα, Anti-HPV-16,Month 12(N=71,66,70)	884 (488 to 1924)	527 (210 to 1033)	725 (383 to 1445)	
CD4-d-TNFα, Anti-HPV-18,Month 12(N=71,68,70)	674 (290 to 1272)	299 (144.5 to 600)	403 (175 to 771)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD8-ALL DOUBLES, Anti-HPV-16, Day 0 (N=57,47,55)	1 (1 to 14)	2 (1 to 43)	1 (1 to 32)	
CD8-ALL DOUBLES, Anti-HPV-18, Day 0 (N=57,46,56)	1 (1 to 10)	1 (1 to 29)	1 (1 to 23.5)	
CD8-ALL DOUBLES, Anti-HPV-16,Month 7(N=68,63,65)	1 (1 to 33)	1 (1 to 40)	1 (1 to 33)	
CD8-ALL DOUBLES, Anti-HPV-18,Month 7(N=67,63,66)	1 (1 to 19)	1 (1 to 37)	1 (1 to 40)	
CD8-ALL DOUBLES, Anti-HPV-16,Month 12(N=71,66,70)	1 (1 to 31)	1 (1 to 44)	1 (1 to 32)	
CD8-ALL DOUBLES, Anti-HPV-18,Month 12(N=71,68,70)	1 (1 to 27)	1 (1 to 32.5)	1 (1 to 20)	
CD8-d-CD40L, Anti-HPV-16, Day 0 (N=57,47,55)	1 (1 to 1)	1 (1 to 3)	1 (1 to 1)	
CD8-d-CD40L, Anti-HPV-18, Day 0 (N=57,46,56)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-CD40L, Anti-HPV-16,Month 7(N=68,63,65)	1 (1 to 1)	1 (1 to 28)	1 (1 to 24)	
CD8-d-CD40L, Anti-HPV-18,Month 7(N=67,63,66)	1 (1 to 1)	1 (1 to 24)	1 (1 to 20)	
CD8-d-CD40L, Anti-HPV-16,Month 12(N=71,66,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 3)	
CD8-d-CD40L, Anti-HPV-18,Month 12(N=71,68,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/ million cells				
median (inter-quartile range (Q1-Q3))				
CD8-d-IFNγ, Anti-HPV-16, Day 0 (N=57,47,55)	1 (1 to 1)	1 (1 to 36)	1 (1 to 30)	
CD8-d-IFNγ, Anti-HPV-18, Day 0 (N=57,46,56)	1 (1 to 2)	1 (1 to 24)	1 (1 to 14)	
CD8-d-IFNγ, Anti-HPV-16,Month 7(N=68,63,65)	1 (1 to 31)	1 (1 to 36)	1 (1 to 30)	
CD8-d-IFNγ, Anti-HPV-18,Month 7(N=67,63,66)	1 (1 to 1)	1 (1 to 27)	1 (1 to 28)	
CD8-d-IFNγ, Anti-HPV-16,Month 12(N=71,66,70)	1 (1 to 28)	1 (1 to 29)	1 (1 to 28)	
CD8-d-IFNγ, Anti-HPV-18, Month 12 (N=71,68,70)	1 (1 to 26)	1 (1 to 32.5)	1 (1 to 10)	
CD8-d-IL-2, Anti-HPV-16, Day 0 (N=57,47,55)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-18,Day 0 (N=57,46,56)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-16,Month 7(N=68,63,65)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-18,Month 7(N=67,63,66)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-16,Month 12(N=71,66,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-18,Month 12(N=71,68,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD8-d-TNFα, Anti-HPV-16, Day 0 (N=57,47,55)	1 (1 to 1)	1 (1 to 36)	1 (1 to 22)	

CD8-d-TNFα, Anti-HPV-18, Day 0 (N=57,46,56)	1 (1 to 25)	1 (1 to 30)	1 (1 to 13.5)	
CD8-d-TNFα, Anti-HPV-16,Month 7(N=68,63,65)	1 (1 to 26)	1 (1 to 25)	1 (1 to 22)	
CD8-d-TNFα, Anti-HPV-18,Month 7(N67,63,66)	1 (1 to 1)	1 (1 to 1)	1 (1 to 23)	
CD8-d-TNFα, Anti-HPV-16,Month 12(N=71,66,70)	1 (1 to 1)	1 (1 to 25)	1 (1 to 29)	
CD8-d-TNFα, Anti-HPV-18,Month 12(N=71,68,70)	1 (1 to 8)	1 (1 to 21.5)	1 (1 to 24)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Month 24

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD4+ All doubles, Anti-HPV-16,Month 24(N=66,65,71)	1097 (489 to 2410)	738 (360 to 1109)	974 (573 to 1838)	
CD4+ All doubles, Anti-HPV-18,Month 24(N=65,65,70)	630 (301 to 1383)	348 (202 to 549)	561.5 (258 to 972)	
CD4-d-CD40L, Anti-HPV-16,Month 24(N=66,65,71)	1083 (510 to 2269)	734 (346 to 1084)	964 (582 to 1802)	
CD4-d-CD40L, Anti-HPV-18,Month 24(N=65,65,70)	587 (282 to 1344)	333 (206 to 534)	563.5 (289 to 940)	
CD4-d- IFNγ, Anti-HPV-16,Month 24(N=66,65,71)	276 (111 to 781)	315 (128 to 519)	431 (157 to 777)	
CD4-d- IFNγ, Anti-HPV-18,Month 24(N=65,65,70)	169 (59 to 440)	106 (51 to 227)	218 (63 to 362)	
CD4-d-IL-2, Anti-HPV-16,Month 24(N=66,65,71)	879.5 (429 to 1711)	574 (280 to 898)	687 (479 to 1480)	
CD4-d-IL-2, Anti-HPV-18,Month 24(N=65,65,70)	494 (238 to 926)	248 (138 to 415)	400.5 (206 to 713)	
CD4-d-TNFα, Anti-HPV-16,Month 24(N=66,65,71)	755 (375 to 1668)	524 (235 to 876)	791 (416 to 1516)	
CD4-d-TNFα, Anti-HPV-18,Month 24(N=65,65,70)	479 (183 to 1036)	238 (130 to 478)	519 (228 to 793)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Month 24

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	68	70	
Units: T cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD8-ALL DOUBLES, Anti-HPV-16,Month 24(N=66,65,71)	1 (1 to 29)	1 (1 to 1)	1 (1 to 2)	
CD8-ALL DOUBLES, Anti-HPV-18,Month 24(N=65,65,70)	1 (1 to 30)	1 (1 to 30)	1 (1 to 31)	
CD8-d-CD40L, Anti-HPV-16,Month 24(N=66,65,71)	1 (1 to 23)	1 (1 to 1)	1 (1 to 1)	
CD8-d-CD40L, Anti-HPV-18,Month 24(N=65,65,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 23)	
CD8-d-IFNγ, Anti-HPV-16,Month 24(N=66,65,71)	1 (1 to 19)	1 (1 to 1)	1 (1 to 3)	
CD8-d-IFNγ, Anti-HPV-18,Month 24(N=65,65,70)	1 (1 to 1)	1 (1 to 23)	1 (1 to 23)	
CD8-d-IL-2, Anti-HPV-16,Month 24(N=66,65,71)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-18,Month 24(N=65,65,70)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-TNFα, Anti-HPV-16,Month 24(N=66,65,71)	1 (1 to 27)	1 (1 to 1)	1 (1 to 1)	
CD8-d-TNFα, Anti-HPV-18,Month 24(N=65,65,70)	1 (1 to 18)	1 (1 to 23)	1 (1 to 21)	

Statistical analyses

No statistical analyses for this end point

Secondary: B-cell-mediated immune responses in the sub-cohort for CMI

End point title	B-cell-mediated immune responses in the sub-cohort for CMI

End point description:

The frequency of B-cell Elispot response to HPV-16/18 by overall status was presented.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12 and 24

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	72	80	
Units: B cells/million cells				
median (inter-quartile range (Q1-Q3))				
HPV-16, PRE (N=74,59,73)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
HPV-18, PRE (N=74,59,73)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
HPV-16, M7 (N=76,72,80)	1605.5 (593.5 to 3483.5)	1097.5 (449 to 2068)	687 (115.5 to 1966.5)	
HPV-18, M7 (N=76,72,80)	593.5 (103.5 to 1771)	80 (0 to 376)	111 (0 to 391)	
HPV-16, M12 (N=56,56,57)	396.5 (89 to 1044)	248 (61.5 to 756)	281 (47 to 974)	
HPV-18, M12 (N=56,56,57)	252 (77 to 635)	67 (0 to 182.5)	65 (0 to 220)	
HPV-16, M24 (N=52,50,61)	254.5 (13 to 706)	204 (16 to 578)	256 (68 to 600)	
HPV-18, M24 (N=52,50,61)	125.5 (31 to 370.5)	45 (0 to 143)	110 (0 to 287)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited local symptoms

End point title	Number of subjects with any, grade 3 and related solicited local symptoms

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimetres (mm) of injection site. Relationship analysis was not performed.

End point type	Secondary

End point timeframe:

During the 7-day period (Days 0-6) following vaccination (across doses)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	357	356	
Units: Subjects				
Any Pain	329	276	295	
Grade 3 Pain	42	17	18	
Any Redness	191	134	157	
Grade 3 Redness	0	0	2	
Any Swelling	163	98	118	
Grade 3 Swelling	5	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related solicited general symptoms

End point title	Number of subjects with any, grade 3 and related solicited general symptoms

End point description:

Assessed solicited general symptoms were arthralgia, fatigue, gastrointestinal symptoms, headache, myalgia, rash, temperature [defined as oral temperature equal to or above 37.5 degrees Celsius (°C)] and urticaria. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever > 39.0 °C. Related = symptom assessed by the investigator as related to the vaccination.

End point type	Secondary

End point timeframe:

During the 7-day period (Days 0-6) following vaccination (across doses)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	357	356	
Units: Subjects				
Any Arthralgia	68	81	67	
Grade 3 Arthralgia	6	4	1	
Related Arthralgia	51	55	51	
Any Fatigue	192	199	193	
Grade 3 Fatigue	18	15	7	
Related Fatigue	151	151	143	
Any Gastrointestinal	55	74	69	
Grade 3 Gastrointestinal	5	6	3	
Related Gastrointestinal	31	49	40	
Any Headache	147	133	151	
Grade 3 Headache	17	7	4	
Related Headache	106	88	100	
Any Myalgia	166	143	136	
Grade 3 Mylagia	8	8	6	

Related Myalgia	128	111	100	
Any Rash	26	16	18	
Grade 3 Rash	0	0	0	
Related Rash	16	10	12	
Any Temperature	53	59	47	
Grade 3 Temperature	7	2	4	
Related Temperature	35	31	30	
Any Urticaria	27	13	25	
Grade 3 Urticaria	4	1	0	
Related Urticaria	15	11	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, grade 3 and related unsolicited adverse events (AEs)

End point title	Number of subjects with any, grade 3 and related unsolicited adverse events (AEs)

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	Secondary

End point timeframe:

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

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects with any AE(s)	91	96	101	
Subjects with any Grade 3 AE(s)	18	8	20	
Subjects with any Related AE(s)	8	14	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with potentially immune mediated diseases (pIMDs)

End point title	Number of subjects with potentially immune mediated diseases (pIMDs)

End point description:

Note: Results beyond Month 24 will be updated when validated results become available.

End point type	Secondary

End point timeframe:

From Day 0 to Month 36 (throughout the study period)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects with any pIMD(s), Month 7	2	1	0	
Subjects with any pIMD(s), Month 12	3	3	0	
Subjects with any pIMD(s), Month 18	3	3	0	
Subjects with any pIMD(s), Month 24	3	3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with medically significant conditions (MSCs)

End point title	Number of subjects with medically significant conditions (MSCs)

End point description:

MSCs were defined as AEs prompting emergency room (ER) or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs 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.

End point type	Secondary

End point timeframe:

From Day 0 to Month 36 (throughout the study period)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects with any MSC(s), Month 7	43	49	39	
Subjects with any MSC(s), Month 12	52	57	47	
Subjects with any MSC(s), Month 18	65	64	54	
Subjects with any MSC(s), Month 24	71	75	56	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Serious Adverse Events (SAEs)

End point title	Number of subjects with Serious Adverse Events (SAEs)

End point description:

SAEs assessed include medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary

End point timeframe:

From Day 0 to Month 36 (throughout the study period)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Any SAE(s)	21	11	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects starting a concomitant medication

End point title	Number of subjects starting a concomitant medication

End point description:

The outcome presents the number of subjects starting any concomitant medication, as well as any antipyretic, any prophylactic antipyretic and any antibiotic.

End point type	Secondary

End point timeframe:

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

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Any concomitant medication	127	126	129	
Any antipyretic	76	86	81	
Any antibiotic	23	27	33	
Prophylactic antipyretic	5	2	2	
Prophylactic antibiotic	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects starting a concomitant medication

End point title	Number of subjects starting a concomitant medication

End point description:

The outcome presents the number of subjects starting any concomitant medication, as well as any antipyretic, any prophylactic antipyretic and any antibiotic.

End point type	Secondary

End point timeframe:

From Day 0 to Month 36 (throughout the study period)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	354	
Units: Subjects				
Any antipyretic, M7 [N=359,358,354]	68	74	71	
Any concomitant medication, M7 [N=359,358,354]	127	127	129	
Any antibiotic, M7 [N=359,358,354]	23	27	32	
Any concomitant medication, M12 [N=356,348,350]	158	138	153	
Any antipyretic, M12 [N=356,348,350]	90	80	81	
Any antibiotic, M12 [N=356,348,350]	37	33	43	
Any concomitant medication, M18 [N=356,347,349]	158	138	153	
Any antipyretic, M18 [N=356,347,349]	90	80	81	
Any antibiotic, M18 [N=356,347,349]	37	33	43	
Prophylactic antipyretic, M12 [N=356,348,350]	5	2	2	
Prophylactic antipyretic, M18 [N=356,347,349]	5	2	2	
Any concomitant medication, M24 [N=355,344,349]	163	146	157	
Any antipyretic, M24 [N=355,344,349]	94	82	80	
Prophylactic antipyretic, M24 [N=356,347,349]	5	2	2	
Any antibiotic, M24 [N=355,344,349]	43	38	158	
Any concomitant medication, M36 [N=351,339,346]	166	147	94	
Any antipyretic, M36 [N=351,339,346]	105	97	94	
Prophylactic antipyretic, M36 [N=351,339,346]	5	2	2	
Any antibiotic, M36 [N=351,339,346]	48	40	49	

Prophylactic antibiotic, M36 [N=351,339,346]	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects completing the vaccination schedule

End point title	Number of subjects completing the vaccination schedule

End point description:

The number of subjects who have completed the three-dose vaccination schedule in all groups.

End point type	Secondary

End point timeframe:

Throughout the study period (From Day 0 up to Month 36)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects receiving all 3 vaccine doses	357	352	354	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pregnancies

End point title	Number of subjects with pregnancies

End point description:

Note: No pregnancies were reported up to the Month 36 time point.

End point type	Secondary

End point timeframe:

Throughout the study period (From Day 0 up to Month 36)

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects with any pregnancy, M12	0	0	0	
Subjects with any pregnancy, M18	0	0	0	
Subjects with any pregnancy, M24	0	0	0	
Subjects with any pregnancy, M36	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates assessed by ELISA

End point title	Anti-HPV-16/18 seroconversion rates assessed by ELISA

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to 19 and 18 EL.U/mL, respectively) in the serum of subjects seronegative before vaccination in the primary study.

End point type	Secondary

End point timeframe:

At Month 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	313	321	
Units: Subjects				
Anti-HPV-16, Month 36 (N=324,313,321)	324	310	320	
Anti-HPV-18, Month 36 (N=324,313,321)	324	270	298	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates assessed by PBNA in a subset of subjects

End point title	Anti-HPV-16/18 seroconversion rates assessed by PBNA in a subset of subjects

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to ≥ 40 ED50) in the serum of subjects seronegative before vaccination in the primary study.
The analysis was based on the ATP cohort for immunogenicity, which included all evaluable subjects for

whom immunogenicity data were available at the time of the analysis.

End point type	Secondary

End point timeframe:

At Months 24 and 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	92	
Units: Subjects				
Anti-HPV-16, Month 24 (N=88,88,92)	88	88	91	
Anti-HPV-18, Month 24 (N=88,86,92)	88	77	89	
Anti-HPV-16, Month 36 (N=89,87,91)	89	87	91	
Anti-HPV-18, Month 36 (N=89,87,91)	89	75	86	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point title	Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point description:

Anti-HPV 16/18 antibody titers were presented as geometric mean titers (GMTs) and expressed in titers using the PBNA.
The analysis was based on the ATP cohort for immunogenicity, which included all evaluable subjects for whom immunogenicity data were available at the time of the analysis.

End point type	Secondary

End point timeframe:

At Months 24 and 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	89	88	92	
Units: Titer				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Month 24 (N=88,88,92)	5059.5 (4112.2 to 6225.1)	1138.1 (845.5 to 1531.9)	1965.5 (1510.6 to 2557.3)	
Anti-HPV-18, Month 24 (N=88,86,92)	1725.1 (1359.3 to 2189.4)	234.6 (175.8 to 313.2)	568 (419 to 770.1)	
Anti-HPV-16, Month 36 (N=89,87,91)	4357.8 (3577.8 to 5307.9)	1071.7 (811.2 to 1415.7)	1577 (1210.4 to 2054.5)	

Anti-HPV-18, Month 36 (N=89,87,91)	1613.9 (1267.6 to 2054.7)	185.8 (140.4 to 245.8)	472.8 (345.8 to 646.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: T-cell-mediated immune responses in the sub-cohort for CMI

End point title	T-cell-mediated immune responses in the sub-cohort for CMI

End point description:

Immune markers expressed were among Interleukin-2 (IL-2), Interferon-gamma (IFN-γ), Tumour necrosis factor-alpha (TNF-α) and CD40-ligand (CD40-L).

End point type	Secondary

End point timeframe:

At Month 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	55	64	
Units: T-cells/million cells				
median (inter-quartile range (Q1-Q3))				
CD4+ All doubles, Anti-HPV-16,Month 36(N=58,55,64)	1012 (427 to 2373)	685 (385 to 1321)	842.5 (437.5 to 1624)	
CD4+ All doubles, Anti-HPV-18,Month 36(N=57,55,63)	682 (313 to 1425)	350 (196 to 665)	516 (270 to 1029)	
CD4-d-CD40L, Anti-HPV-16, Month 36 (N=58,55,64)	957 (465 to 2303)	685 (349 to 1321)	778.5 (416.5 to 1560.5)	
CD4-d-CD40L, Anti-HPV-18, Month 36 (N=57,55,63)	671 (290 to 1435)	337 (204 to 648)	499 (264 to 1020)	
CD4-d-IFNγ, Anti-HPV-16, Month 36 (N=58,55,64)	253.5 (81 to 667)	301 (134 to 571)	270.5 (129 to 666.5)	
CD4-d-IFNγ, Anti-HPV-18, Month 36 (N=57,55,63)	193 (51 to 376)	109 (27 to 230)	155 (45 to 314)	
CD4-d-IL-2, Anti-HPV-16, Month 36 (N=58,55,64)	784 (331 to 1673)	517 (295 to 1014)	680 (308 to 1245.5)	
CD4-d-IL-2, Anti-HPV-18, Month 36 (N=57,55,63)	507 (213 to 1069)	274 (137 to 467)	341 (168 to 798)	
CD4-d-TNFα, Anti-HPV-16, Month 36 (N=58,55,64)	786.5 (343 to 1930)	547 (282 to 1005)	724.5 (368 to 1338)	
CD4-d-TNFα, Anti-HPV-18, Month 36 (N=57,55,63)	588 (250 to 1138)	301 (120 to 453)	479 (200 to 808)	
CD8- All doubles, Anti-HPV-16,Month 36(N=58,55,64)	1 (1 to 48)	1 (1 to 28)	1 (1 to 38.5)	
CD8- All doubles, Anti-HPV-18,Month 36(N=57,55,63)	4 (1 to 40)	2 (1 to 41)	1 (1 to 28)	
CD8-d-CD40L, Anti-HPV-16, Month 36 (N=58,55,64)	1 (1 to 31)	1 (1 to 24)	1 (1 to 29)	
CD8-d-CD40L, Anti-HPV-18, Month 36 (N=57,55,63)	1 (1 to 6)	1 (1 to 27)	1 (1 to 28)	

CD8-d-IFNγ, Anti-HPV-16, Month 36 (N=58,55,64)	1 (1 to 47)	1 (1 to 25)	1 (1 to 33)	
CD8-d-IFNγ, Anti-HPV-18, Month 36 (N=57,55,63)	1 (1 to 31)	2 (1 to 40)	1 (1 to 25)	
CD8-d-IL-2, Anti-HPV-16, Month 36 (N=58,55,64)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-IL-2, Anti-HPV-18, Month 36 (N=57,55,63)	1 (1 to 1)	1 (1 to 1)	1 (1 to 1)	
CD8-d-TNFα, Anti-HPV-16, Month 36 (N=58,55,64)	1 (1 to 24)	1 (1 to 1)	1 (1 to 26)	
CD8-d-TNFα, Anti-HPV-18, Month 36 (N=57,55,63)	1 (1 to 31)	1 (1 to 21)	1 (1 to 12)	

Statistical analyses

No statistical analyses for this end point

Secondary: B-cell-mediated immune responses in the sub-cohort for CMI

End point title	B-cell-mediated immune responses in the sub-cohort for CMI

End point description:

The frequency of B-cell Elispot response to HPV-16/18 by overall status was presented.

End point type	Secondary

End point timeframe:

At Month 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	54	53	
Units: B cells/million cells				
median (inter-quartile range (Q1-Q3))				
HPV-16, M36 (N=59,54,53)	353 (91 to 927)	382.5 (166 to 614)	246 (21 to 565)	
HPV-18, M36 (N=59,54,53)	116 (1 to 329)	25 (1 to 228)	63 (1 to 150)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with medically significant conditions (MSCs)

End point title	Number of subjects with medically significant conditions (MSCs)

End point description:

MSCs were defined as AEs prompting emergency room (ER) or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs 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.

End point type	Secondary

End point timeframe:

At Month 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	359	358	358	
Units: Subjects				
Subjects with Any MSC(S), Month 36	77	79	63	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 seroconversion rates assessed by PBNA in a subset of subjects

End point title	Anti-HPV-16/18 seroconversion rates assessed by PBNA in a subset of subjects

End point description:

Seroconversion was defined as the appearance of antibodies (i.e. anti-HPV-16 and anti-HPV-18 antibody titers greater than or equal to ≥ 40 ED50) in the serum of subjects seronegative before vaccination in the primary study.
The analysis was based on the Total Vaccinated cohort, which included all subjects with at least one study vaccine administered, on subjects with
symptom sheets completed.

End point type	Secondary

End point timeframe:

At Months 24 and 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	92	99	
Units: Subjects				
Anti-HPV-16, Month 24 (N=96,91,99)	95	91	98	
Anti-HPV-18, Month 24 (N=96,89,99)	96	80	95	
Anti-HPV-16, Month 36 (N=98,92,98)	97	92	98	
Anti-HPV-18, Month 36 (N=97,92,98)	97	80	92	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point title	Anti-HPV-16/18 antibody titers assessed by PBNA in a subset of subjects

End point description:

Anti-HPV 16/18 antibody titers were presented as geometric mean titers (GMT) and expressed in titers using the PBNA.
The analysis was based on the Total Vaccinated cohort, which included all subjects with at least one study vaccine administered, on subjects with
symptom sheets completed.

End point type	Secondary

End point timeframe:

At Months 24 and 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	92	99	
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Month 24 (N=96,91,99)	4609.1 (3673.5 to 5782.9)	1133.9 (848.1 to 1516)	1948.1 (1515 to 2505)	
Anti-HPV-18, Month 24 (N=96,89,99)	1638.6 (1297.9 to 2068.8)	237.2 (179.1 to 314.3)	573 (425 to 772.5)	
Anti-HPV-16, Month 36 (N=98,92,98)	4011.7 (3229.7 to 4983)	1058.4 (806.3 to 1389.2)	1517.2 (1174.7 to 1959.4)	
Anti-HPV-18, Month 36 (N=97,92,98)	1513.7 (1197.5 to 1913.2)	185.8 (142.2 to 242.7)	468.6 (346.3 to 634)	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point title	Anti-HPV-16/18 antibody concentrations assessed by ELISA

End point description:

Anti-HPV 16/18 antibody concentrations were presented as geometric mean concentrations (GMC) and expressed in ELISA units per milliliter (EL.U/mL) based on ELISA.

End point type	Secondary

End point timeframe:

At Month 36

End point values	Cervarix 2 dose Group	Gardasil 2 dose Group	Gardasil 3 dose Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	324	313	321	
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Month 36 (N=324,313,321)	1068.9 (979.6 to 1166.5)	375.4 (329.6 to 427.5)	475.3 (428.7 to 527)	
Anti-HPV-18, Month 36 (N=324,313,321)	487.8 (439.3 to 541.8)	71.3 (62.3 to 81.5)	120.2 (104.3 to 138.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: up to Day 7 post vaccination. AEs: up to Day 30 post vaccination. SAEs throughout the study period (up to Month 36).

Adverse event reporting additional description:

For the systematically assessed other (non-serious) adverse events, the number of participants at risk included those from Total Vaccinated cohort who had the symptom sheet completed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cervarix 2 dose Group

Reporting group description:

Subjects who received 2 doses of Cervarix™ vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

Reporting group title	Gardasil 3 dose Group

Reporting group description:

Subjects who received 3 doses of Gardasil® vaccine at Day 0 and at Months 2 and 6. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

Reporting group title	Gardasil 2 dose Group

Reporting group description:

Subjects who received 2 doses of Gardasil® vaccine at Day 0 and Month 6 and 1 dose of placebo at Month 2. The vaccines were administered intramuscularly, in the deltoid muscle of the non-dominant upper arm.

Serious adverse events	Cervarix 2 dose Group	Gardasil 3 dose Group	Gardasil 2 dose Group
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 359 (5.85%)	14 / 358 (3.91%)	11 / 358 (3.07%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Teratoma			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			

subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous incomplete			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic shock			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval ulceration			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 359 (0.56%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (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
Depression			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	2 / 359 (0.56%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			

subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo positional			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth cyst			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema nodosum			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			

subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-barr virus infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	3 / 359 (0.84%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 359 (0.00%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 359 (0.28%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 358 (0.00%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 359 (0.56%)	1 / 358 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 359 (0.00%)	0 / 358 (0.00%)	1 / 358 (0.28%)
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 2 dose Group	Gardasil 3 dose Group	Gardasil 2 dose Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	329 / 359 (91.64%)	295 / 358 (82.40%)	276 / 358 (77.09%)
General disorders and administration site conditions			
Pain			
subjects affected / exposed	329 / 359 (91.64%)	295 / 358 (82.40%)	276 / 358 (77.09%)
occurrences (all)	329	295	276
Redness			

subjects affected / exposed	191 / 359 (53.20%)	157 / 358 (43.85%)	134 / 358 (37.43%)
occurrences (all)	191	157	134
Swelling			
subjects affected / exposed	163 / 359 (45.40%)	118 / 358 (32.96%)	98 / 358 (27.37%)
occurrences (all)	163	118	98
Arthralgia			
subjects affected / exposed	68 / 359 (18.94%)	67 / 358 (18.72%)	81 / 358 (22.63%)
occurrences (all)	68	67	81
Fatigue			
subjects affected / exposed	192 / 359 (53.48%)	193 / 358 (53.91%)	199 / 358 (55.59%)
occurrences (all)	192	193	199
Gastrointestinal			
subjects affected / exposed	55 / 359 (15.32%)	69 / 358 (19.27%)	74 / 358 (20.67%)
occurrences (all)	55	69	74
Headache			
subjects affected / exposed	147 / 359 (40.95%)	151 / 358 (42.18%)	133 / 358 (37.15%)
occurrences (all)	147	151	133
Myalgia			
subjects affected / exposed	166 / 359 (46.24%)	136 / 358 (37.99%)	143 / 358 (39.94%)
occurrences (all)	166	136	143
Rash			
subjects affected / exposed	26 / 359 (7.24%)	18 / 358 (5.03%)	16 / 358 (4.47%)
occurrences (all)	26	18	16
Temperature			
subjects affected / exposed	53 / 359 (14.76%)	47 / 358 (13.13%)	59 / 358 (16.48%)
occurrences (all)	53	47	59
Urticaria			
subjects affected / exposed	27 / 359 (7.52%)	25 / 358 (6.98%)	13 / 358 (3.63%)
occurrences (all)	27	25	13
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	27 / 359 (7.52%)	31 / 358 (8.66%)	29 / 358 (8.10%)
occurrences (all)	27	31	29
Nasopharyngitis			
subjects affected / exposed	8 / 359 (2.23%)	20 / 358 (5.59%)	11 / 358 (3.07%)
occurrences (all)	8	20	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2012	Amendment 1 At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator will have full authority to break the treatment code
24 June 2014	Amendment 3 At the time of study initiation, Cervarix was approved to be administered according to a 3-dose vaccination schedule. Subjects belonging to the study groups HPV_2D and Gard_2D received two doses of either Cervarix or Gardasil during the primary study epoch. These subjects were to be offered a third dose of the vaccine that they received, at the end of the study, at Month 36. Recently, the 2-dose schedule of Cervarix and Gardasil has been approved in some countries, and hence the protocol is being amended to reflect that a third dose of the vaccine that they received will be offered to the subjects in the two 2-dose groups (HPV_2D and Gard_2D) only if required based on local prescribing recommendations. In addition, the indication for Cervarix and the list of contributing authors have been updated. The number of countries in which Cervarix and Gardasil are licensed has been updated. Minor changes have been made in a few sections to correct typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported