Clinical trial results:
A Phase IIIb open-label, randomised, multi-centre primary immunization study to evaluate the immunogenicity and safety of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine when administered intramuscularly according to alternative 2-dose schedules in 9 - 14 year old healthy females compared to the standard 3-dose schedule for GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine in 15 - 25 year old healthy females

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-000757-22
Trial protocol	DE IT
Global end of trial date	13 November 2014

Results information

Result version number	v2
This version publication date	06 April 2016
First version publication date	28 May 2015
Version creation reason	• New data added to full data set • Correction of full data set Correction of full data set: Data correction due to a system error in EudraCT – Results. Addition of secondary results.

Trial information

Trial identification

Sponsor protocol code	114700

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01381575
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	28 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2012
Global end of trial reached?	Yes
Global end of trial date	13 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the immunogenicity (as determined by ELISA) of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered according to a 2-dose schedule of 0,6 months in 9-14 year old females is non-inferior to that administered according to the standard 3-dose schedule of 0,1,6 months in 15-25 year old females,1 month after the last dose of study vaccine.

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. For this reason, the vaccine remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 190
Country: Number of subjects enrolled	Taiwan: 318
Country: Number of subjects enrolled	Thailand: 314
Country: Number of subjects enrolled	Germany: 325
Country: Number of subjects enrolled	Italy: 300
Worldwide total number of subjects	1447
EEA total number of subjects	625

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)	1032
Adults (18-64 years)	415
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cervarix 1 Group

Arm description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 6. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects will receive 2 or 3 doses of HPV vaccine administered intramuscularly

Arm title	Cervarix 2 Group

Arm description:

Female subjects aged 15 to 25 years at the time of the first vaccination, who received 3 doses of the Cervarix vaccine at Months 0, 1 and 6, respectively. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects will receive 2 or 3 doses of HPV vaccine administered intramuscularly

Arm title	Cervarix 3 Group

Arm description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 12. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Arm type	Experimental

Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects will receive 2 or 3 doses of HPV vaccine administered intramuscularly

Number of subjects in period 1	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group
Started	550	482	415
Completed	548	472	408
Not completed	2	10	7
Consent withdrawn by subject	-	-	4
Adverse event, non-fatal	-	-	1
Protocol violation	-	-	1
Unspecified	2	10	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cervarix 1 Group
Reporting group description:	
Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 6. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.	
Reporting group title	Cervarix 2 Group
Reporting group description:	
Female subjects aged 15 to 25 years at the time of the first vaccination, who received 3 doses of the Cervarix vaccine at Months 0, 1 and 6, respectively. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.	
Reporting group title	Cervarix 3 Group
Reporting group description:	
Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 12. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.	

Reporting group values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group
Number of subjects	550	482	415
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	11.6	19.6	11.4
standard deviation	± 1.59	± 3.05	± 1.55
Gender categorical Units: Subjects			
Female	550	482	415
Male	0	0	0

Reporting group values	Total		
Number of subjects	1447		
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	1447		
Male	0		

End points

End points reporting groups

Reporting group title	Cervarix 1 Group

Reporting group description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 6. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Reporting group title	Cervarix 2 Group

Reporting group description:

Female subjects aged 15 to 25 years at the time of the first vaccination, who received 3 doses of the Cervarix vaccine at Months 0, 1 and 6, respectively. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Reporting group title	Cervarix 3 Group

Reporting group description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 12. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Primary: Number of seroconverted subjects for Anti- Human Papilloma virus 16 (Anti-HPV-16) and Anti-Human Papilloma Virus 18 (Anti-HPV-18) antibodies

End point title	Number of seroconverted subjects for Anti- Human Papilloma virus 16 (Anti-HPV-16) and Anti-Human Papilloma Virus 18 (Anti-HPV-18) antibodies[1]

End point description:

Seroconversion was defined as the appearance of antibodies (anti-HPV-16 titres ≥ 8 ELISA units per millilitre (EL.U/mL) and anti-HPV-18 titres ≥ 7 EL.U/mL) in the serum of subjects seronegative before vaccination. A seronegative subject was a subject with anti-HPV-16/18 antibody concentration < 8/7 EL.U/mL. A seropositive subject was a subject with anti-HPV-16/18 antibody concentration ≥ 8/7

End point type	Primary

End point timeframe:

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

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	382		
Units: Subjects				
Anti-HPV-16 [N= 488, 352]	488	352		
Anti-HPV-18 [N=493, 382]	493	382		

Statistical analyses

Statistical analysis title	Difference in seroconversion rate HPV-16

Statistical analysis description:

To demonstrate that the immunogenicity (as determined by [enzyme-linked immunosorbent assay]

ELISA) of HPV vaccine administered according to a 2-dose schedule of 0, 6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0, 1, 6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

Comparison groups	Cervarix 2 Group v Cervarix 1 Group
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.78

Notes:

[2] - Non-inferiority with respect to seroconversion was considered to be demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of the 95% Confidence Interval (CI) for the difference (0,1,6M Group minus 0,6M Group) was below 5%.

Statistical analysis title	Difference in seroconversion rate HPV-18

Statistical analysis description:

To demonstrate that the immunogenicity (as determined by [enzyme-linked immunosorbent assay] ELISA) of HPV vaccine administered according to a 2-dose schedule of 0, 6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0, 1, 6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

Comparison groups	Cervarix 1 Group v Cervarix 2 Group
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.77

Notes:

[3] - Non-inferiority with respect to seroconversion was considered to be demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of the 95% Confidence Interval (CI) for the difference (0,1,6M Group minus 0,6M Group) was below 5%.

Primary: Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).

End point title	Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).[4]

End point description:

Antibody concentrations were and expressed as geometric mean concentrations (GMCs) and expressed as enzyme-linked immunosorbent assay [ELISA] units per millilitre (EL.U/mL), with the cut-off values of 8 EL.U/mL for HPV-016 and 7 EL.U/mL for HPV-018.

End point type	Primary

End point timeframe:

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

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	432		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16 [N= 540, 432]	9413.3 (8853.4 to 10008.7)	9970.7 (9128.3 to 10890.9)		
Anti-HPV-18 [N=536, 432]	5968.8 (5580.3 to 6384.3)	4880.3 (4486.4 to 5308.8)		

Statistical analyses

Statistical analysis title	GMT ratio HPV-16

Statistical analysis description:

To demonstrate that the immunogenicity (as determined by [enzyme-linked immunosorbent assay] ELISA) of HPV vaccine administered according to a 2-dose schedule of 0, 6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0, 1, 6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

Comparison groups	Cervarix 1 Group v Cervarix 2 Group
Number of subjects included in analysis	972
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	GMT ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.22

Notes:

[5] - Non-inferiority with respect to geometric mean titres (GMTs) was demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of 95% CI for the GMT ratio (0,1,6M Group divided by 0,6,M Group) was below 2.

Statistical analysis title	GMT ratio HPV-18

Statistical analysis description:

To demonstrate that the immunogenicity (as determined by [enzyme-linked immunosorbent assay] ELISA) of HPV vaccine administered according to a 2-dose schedule of 0, 6 months in 9-14 year old females was non-inferior to that administered according to the standard 3-dose schedule of 0, 1, 6 months in 15-25 year old females, 1 month after the last dose of study vaccine.

Comparison groups	Cervarix 1 Group v Cervarix 2 Group
Number of subjects included in analysis	972
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	GMT ratio
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	0.95

Notes:

[6] - Non-inferiority with respect to geometric mean titres (GMTs) was demonstrated if, 1 month after the last dose, for both anti-HPV-16 and anti-HPV-18, the upper limit of 95% CI for the GMT ratio (0,1,6M Group divided by 0,6,M Group) was below 2.

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

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

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = Occurrence of any solicited local symptom regardless of their intensity grade. Grade 3 pain = Significant pain at rest, that prevented normal every day activity. Grade 3 redness/swelling = Redness/swelling above 50 millimeters (mm).

End point type	Secondary

End point timeframe:

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

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	480	413	
Units: Subjects				
Any Pain	499	461	381	
Grade 3 Pain	50	53	48	
Any Redness	247	212	197	
Grade 3 Redness	4	10	3	
Any Swelling	225	204	171	
Grade 3 Swelling	5	6	6	

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, fever and urticaria. Any = Occurrence of any solicited general symptom regardless of intensity grade or relationship to vaccination. Any Fever = Axillary temperature equal to or above (≥) 37.5 degrees Celsius (°C). Grade 3 symptom = Symptom that prevented normal activity. Grade 3 fever = Fever > 39.0 °C. Related = General symptom assessed by the investigator as causally related to the vaccination.

End point type	Secondary

End point timeframe:

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

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	480	413	
Units: Subjects				
Any Artharlgia	111	107	93	
Grade 3 Arthralgia	9	6	6	
Related Arthralgia	105	102	83	
Any Fatigue	247	310	215	
Grade 3 Fatigue	14	25	21	
Related Fatigue	221	294	185	
Any Gastrointestinal symptoms	98	134	77	
Grade 3 Gastrointestinal symptoms	7	11	7	
Related Gastrointestinal symptoms	77	106	62	
Any Headache	204	246	185	
Grade 3 Headache	19	26	16	
Related Headache	176	219	148	
Any Myalgia	278	295	221	
Grade 3 Myalgia	24	25	15	
Related Myalgia	265	285	201	
Any Rash	33	25	29	
Grade 3 Rash	2	0	0	
Related Rash	26	18	28	
Any Fever	41	48	42	
Grade 3 Fever	2	3	1	
Related Fever	29	39	32	
Any Urticaria	15	15	13	
Grade 3 Urticaria	1	1	0	
Related Urticaria	13	11	12	

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 = Any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 = Unsolicited AE preventing normal activity. Related = Unsolicited AE assessed by the investigator as causally related to the study vaccination.

End point type	Secondary

End point timeframe:

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

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	482	415	
Units: Subjects				
Any unsolicited AEs	99	165	74	
Grade 3 unsolicited AEs	2	17	6	
Related unsolicited AEs	11	24	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any potential Immune-Mediated Diseases (pIMDs)

End point title	Number of subjects with any potential Immune-Mediated Diseases (pIMDs)

End point description:

pIMDs are a subset of AEs that include both clearly autoimmune diseases and also other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology. Note: Results up to Months 24 and 36 will be updated once they become available.

End point type	Secondary

End point timeframe:

From Day 0 up to Months 7, 13, 24 and 36

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	482	415	
Units: Subjects				
Any pIMDs, up to Month 7	2	1	0	
Any pIMDs, up to Month 13	2	2	2	
Any pIMDs, up to Month 18	2	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects completing the vaccination course

End point title	Number of subjects completing the vaccination course

End point description:

The number of subjects completing the vaccination course was assessed as the number of subjects with at least one dose received during the study.

End point type	Secondary

End point timeframe:

Up to Month 13

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	482	415	
Units: Subjects				
Any Dose received	550	482	415	

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and Anti-HPV-18 antibody titres (by Pseudovirion-Based Neutralisation Assay [PBNA])

End point title	Anti-HPV-16 and Anti-HPV-18 antibody titres (by Pseudovirion-Based Neutralisation Assay [PBNA])[7]

End point description:

Antibody titers were given as Geometric mean titers (GMTs). The cut-off of the assay were ≥ 40 ED50 for anti-HPV-16 and anti-HPV-18. Month 24 validated results will be added once they become available

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: Titer				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Month 0 [N=94]	20 (20 to 20)			
Anti-HPV-16, Month 13 [N=94]	77202.4 (62934.5 to 94705.1)			
Anti-HPV-18, Month 0 [N=94]	20 (20 to 20)			
Anti-HPV-18, Month 13 [N=94]	40052.6 (33593.3 to 47753.8)			

Anti-HPV-16, Month 18 [N=93]	16637.8 (13322.1 to 20778.6)			
Anti-HPV-18, Month 18 [N=93]	9313.7 (7626.1 to 11374.8)			
Anti-HPV-16, Month 24 [N=92]	9964.3 (8169.7 to 12153)			
Anti-HPV-18, Month 24 [N=92]	5373.2 (4340.4 to 6651.8)			
Anti-HPV-16, Month 36 [N=88]	9214.3 (7112.3 to 11937.5)			
Anti-HPV-18, Month 36 [N=88]	4046.4 (3278 to 4994.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and Anti-HPV-18 antibody titres (by Pseudovirion-Based Neutralisation Assay [PBNA])

End point title	Anti-HPV-16 and Anti-HPV-18 antibody titres (by Pseudovirion-Based Neutralisation Assay [PBNA])[8]

End point description:

Antibody titers were given as Geometric mean titers (GMTs). The cut-off of the assay were ≥ 40 ED50 for anti-HPV-16 and anti-HPV-18.Month 24 validated results will be added once they become available

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 18, 24 and 36

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	99		
Units: Titers				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Day 0 [N=103, 99]	21.2 (18.9 to 23.9)	23.2 (20.7 to 26.1)		
Anti-HPV-16, Month 7 [N=103, 99]	77611.5 (63321.3 to 95126.5)	30254.7 (23616.3 to 38759.1)		
Anti-HPV-16, Month 12 [N=101, 98]	14540.1 (11855.1 to 17833.2)	15273.8 (11814.3 to 19746.4)		
Anti-HPV-18, Day 0 [N=103, 99]	21 (19 to 23.3)	22.2 (20.4 to 24.2)		

Anti-HPV-18, Month 7 [N=103, 92]	23276.4 (19557.5 to 27702.6)	13709.2 (10863.6 to 17300.2)		
Anti-HPV-18, Month 12 [N=101, 98]	5703.4 (4609.6 to 7056.8)	5083.3 (3834.2 to 6739.4)		
Anti-HPV-16, Month 18 [N=99,97]	7308.9 (5958 to 8966.1)	8092.7 (6178.6 to 10599.8)		
Anti-HPV-18, Month 18 [N=99,97]	3833.7 (3065.2 to 4795)	2941.7 (2213 to 3910.3)		
Anti-HPV-16, Month 24 [N=99,97]	6181.4 (5104.7 to 7485.3)	7289.7 (5501.1 to 9659.7)		
Anti-HPV-18, Month 24 [N=99,97]	2789 (2230.9 to 3486.7)	2559.9 (1902.2 to 3445.2)		
Anti-HPV-16, Month 36 [N=96,92]	7762.7 (6218.6 to 9690.1)	5063.7 (3800.4 to 6746.9)		
Anti-HPV-18, Month 36 [N=95,92]	2416.4 (1905.9 to 3063.5)	1956.2 (1488.5 to 2570.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for Anti-HPV-16 and Anti-HPV-18 antibodies

End point title	Number of seroconverted subjects for Anti-HPV-16 and Anti-HPV-18 antibodies[9]

End point description:

Seroconversion was defined as the appearance of antibodies (anti-HPV-16 titres ≥ 8 EL.U/mL and anti-HPV-18 titres ≥ 7 EL.U/mL) in the serum of subjects seronegative before vaccination. A seronegative subject was a subject with anti-HPV-16/18 antibody concentration < 8/7 EL.U/mL. A seropositive subject was a subject with anti-HPV-16/18 antibody concentration ≥ 8/7 EL.U/mL.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	369			
Units: Subjects				
Anti-HPV-16, Day 0 (N=355)	0			
Anti-HPV-16, Month 13 (N=355)	355			
Anti-HPV-18, Day 0 (N=369)	0			
Anti-HPV-18, Month 13 (N=369)	369			

Anti-HPV-16, Month 18 (N=353)	353			
Anti-HPV-18, Month 18 (N=366)	366			
Anti-HPV-16, Month 24 (N=346)	346			
Anti-HPV-18, Month 24 (N=360)	360			
Anti-HPV-16, Month 36 (N=339)	339			
Anti-HPV-18, Month 36 (N=355)	355			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).

End point title	Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).[10]

End point description:

Antibody concentrations were expressed as geometric mean titers (GMTs) and given in EL.U/mL, with the cut-off values of ≥ 8 ELISA units per millilitre (EL.U/mL) for HPV-016 and ≥ 7 EL.U/mL for HPV-018.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 18, 24 and 36

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	540	432		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Day 0 [N=540,432]	4.7 (4.5 to 5)	6.1 (5.6 to 6.8)		
Anti-HPV-16, Month 7 [N=540,432]	9413.3 (8853.4 to 10008.7)	9970.7 (9128.3 to 10890.9)		
Anti-HPV-16, Month 12 [N=532,425]	2680.3 (2510.7 to 2861.3)	3377.7 (3077 to 3707.8)		
Anti-HPV-18, Day 0 [N=536,432]	3.9 (3.8 to 4.1)	4.4 (4.1 to 4.8)		
Anti-HPV-18, Month 7 [N=536,432]	5968.8 (5580.3 to 6384.3)	4880.3 (4486.4 to 5308.8)		
Anti-HPV-18, Month 12 [N=528,425]	1559.9 (1446.8 to 1681.8)	1500.7 (1361.3 to 1654.5)		
Anti-HPV-16, Month 18 [N=522,413]	1742.8 (1627.9 to 1865.8)	1986.8 (1803.4 to 2188.8)		
Anti-HPV-18, Month 18 [N=518,413]	891 (822.9 to 964.8)	854.4 (770.9 to 947)		

Anti-HPV-16, Month 24 [N=517,405]	1499.1 (1402 to 1602.9)	1635.3 (1485.2 to 1800.5)		
Anti-HPV-18, Month 24 [N=513,405]	734.3 (679.4 to 793.5)	679.5 (610.8 to 755.9)		
Anti-HPV-16, Month 36 [N=504,399]	1218.4 (1135.4 to 1307.5)	1362.2 (1239.7 to 1496.7)		
Anti-HPV-18, Month 36 [N=500,399]	578.8 (533.4 to 628)	557.4 (502.3 to 618.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for Anti-HPV-16 and Anti-HPV-18 antibodies

End point title	Number of seroconverted subjects for Anti-HPV-16 and Anti-HPV-18 antibodies[11]

End point description:

Seroconversion was defined as the appearance of antibodies (anti-HPV-16 titres ≥ 8 EL.U/mL and anti-HPV-18 titres ≥ 7 EL.U/mL) in the serum of subjects seronegative before vaccination. A seronegative subject was a subject with anti-HPV-16/18 antibody concentration < 8/7 EL.U/mL. A seropositive subject was a subject with anti-HPV-16/18 antibody concentration ≥ 8/7 EL.U/mL.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 18, 24 and 36

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493	382		
Units: Subjects				
Anti-HPV-16, Day 0 [N= 488, 352]	0	0		
Anti-HPV-16, Month 7 [N= 488, 352]	488	352		
Anti-HPV-16, Month 12 [N= 480, 347]	480	347		
Anti-HPV-18, Day 0 [N= 493, 382]	0	0		
Anti-HPV-18, Month 7 [N= 493, 382]	493	382		
Anti-HPV-18, Month 12 [N= 485, 376]	485	376		
Anti-HPV-16, Month 18 [N=473,338]	473	338		
Anti-HPV-18, Month 18 [N= 477,366]	476	366		
Anti-HPV-16, Month 24 [N=468,334]	468	334		
Anti-HPV-18, Month 24 [N=472,362]	471	362		
Anti-HPV-16, Month 36 [N=455,330]	455	330		
Anti-HPV-18, Month 36 [N=462,356]	461	355		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).

End point title	Anti-HPV-16 and anti-HPV-18 antibody concentrations (by ELISA).[12]

End point description:

Antibody concentrations were expressed as geometric mean titers (GMTs) and given in EL.U/mL, with the cut-off values of ≥ 8 ELISA units per millilitre (EL.U/mL) for HPV-16 and ≥ 7 EL.U/mL for HPV-18.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	394			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16, Month 0 [N=394]	4.6 (4.4 to 4.9)			
Anti-HPV-16, Month 13 [N=394]	11290 (10520.9 to 12115.4)			
Anti-HPV-18, Month 0 [N=390]	3.8 (3.7 to 3.9)			
Anti-HPV-18, Month 13 [N=390]	6601 (6116.3 to 7124.1)			
Anti-HPV-16, Month 18 [N=391]	3248 (2991.4 to 3526.6)			
Anti-HPV-18, Month 18 [N=387]	1858.1 (1703 to 2027.2)			
Anti-HPV-16, Month 24 [N=385]	2170.4 (1996.3 to 2359.7)			
Anti-HPV-18, Month 24 [N=381]	1175.7 (1071.7 to 1289.7)			
Anti-HPV-16, Month 36 [N=378]	1544.7 (1424.9 to 1674.6)			
Anti-HPV-18, Month 36 [N=375]	802.1 (732.6 to 878.3)			

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:

MSC include AEs prompting emergency room or physician visits that are not related to common diseases or routine visits for physical examination or vaccination, or serious adverse events (SAEs) that are not related to common diseases. Common diseases include upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervico-vaginal yeast infections, menstrual cycle abnormalities and injury.

End point type	Secondary

End point timeframe:

From Day 0 to Months 7, 13, 18, 24 and 36

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	482	415	
Units: Subjects				
Any MSCs, up to Month 7	75	96	0	
Any MSCs, up to Month 13	99	124	61	
Any MSCs, up to Month 18	112	138	72	
Any MSCs, up to Month 24	113	140	72	
Any MSCs, up to Month 36	134	153	87	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with pregnancies ongoing and their outcome

End point title	Number of subjects with pregnancies ongoing and their outcome

End point description:

Specific pregnancy outcomes were elective termination with apparent congenital anomaly and ectopic pregnancy.

End point type	Secondary

End point timeframe:

From Day 0 up to Months 7, 13, 24 and 36

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	34	1	
Units: Subjects				
Pregnancy ongoing, Month 7	0	7	0	
Elective termination no congenit. anomaly, Month 7	0	1	0	
Ectopic pregnancy, Month 7	0	1	0	
Ectopic pregnancy, Month 13	0	1	0	
Elective termination no congenit.anomaly, Month 13	0	1	0	
Live infant no congenital anomaly, Month 13	0	17	1	
Pregnancy ongoing, Month 13	0	4	0	
Stillbirth no congenital anomaly, Month 13	0	1	0	
Ectopic pregnancy, Month 18	0	1	0	
Elective termination no congenit.anomaly, Month 18	0	1	0	
Live infant no congenit. anomaly, Month 18	0	20	1	
Pregnancy ongoing, Month 18	0	1	0	
Stillbirth no congenit. anomaly, Month 18	0	1	0	
Ectopic pregnancy, Month 24	0	1	0	
Elective termination no congenit.anomaly, Month 24	0	2	0	
Live infant no congenit. anomaly, Month 24	0	23	1	
Pregnancy ongoing, Month 24	1	7	0	
Stillbirth no congenit. anomaly, Month 24	0	1	0	
Ectopic pregnancy, Month 36	0	1	0	
Elective termination no congenit.anomaly, Month 36	0	2	0	
Live infant no congenit. anomaly, Month 36	1	30	1	
Stillbirth no congenit. anomaly, Month 36	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any serious adverse events (SAEs)

End point title	Number of subjects with any serious adverse events (SAEs)

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject. Any was defined as occurrence

of any symptom regardless of intensity grade or relation to vaccination and related was an event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary

End point timeframe:

From Day 0 up to Months 7, 13, 18, 24 and 36

End point values	Cervarix 1 Group	Cervarix 2 Group	Cervarix 3 Group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	550	482	415	
Units: Subjects				
Any SAEs, up to Month 7	6	11	0	
Related SAEs, up to Month 7	0	0	0	
Any SAEs, up to Month 13	12	15	11	
Related SAEs, up to Month 13	0	0	0	
Any SAEs, up to Month 18	14	21	17	
Related SAEs, up to Month 18	0	0	0	
Any SAEs, up to Month 24	14	21	18	
Related SAEs, up to Month 24	0	0	1	
Any SAEs, up to Month 36	20	28	24	
Related SAEs, up to Month 36	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-16 specific T cell-mediated immune response (CMI)

End point title	Cell-mediated immunogenicity related to anti-HPV-16 specific T cell-mediated immune response (CMI)[13]

End point description:

The CMI response was the measure of the cytokines production [i.e.interleukin-2 (IL-2), interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and cluster of differentiation 40 Ligand (CD40L)] by HPV-antigen specific T lymphocytes and measured by intracellular cytokine staining (ICS) assay for HPV-16 The frequency was presented as number of of cytokine-positive cluster of differentiation (CD)4 i.e.CD4+/CD8+ cells per million CD4+/CD8+ cells. All doubles= T cell expressing at least 2 cytokines. Results were tabulated by the pre-vaccination status of the subjects, where S- = seronegative subjects (antibody titre lower than the cut-off value of 8 EL.U/mL) prior to vaccination. S+ = seropositive subjects (antibody titre ≥ 8 El.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	77		
Units: cells/million T cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-16, CD4 all doubles, S-, Day 0 [N=86,72]	88 (56 to 152)	123 (67 to 185.5)		
Anti-HPV-16, CD4 all doubles, S-, Month 7[N=72,54]	3935.5 (1838.5 to 6975.5)	3691 (1889 to 5214)		
Anti-HPV-16, CD4 all doubles, S+, Day 0 [N=10,17]	66 (57 to 189)	87 (60 to 193)		
Anti-HPV-16, CD4 all doubles, S+, Month 7[N=10,16]	4982.5 (1584 to 6610)	1672 (1233.5 to 2600)		
Anti-HPV-16, CD4-d-CD40L, S-, Day 0 [N=86,72]	67.5 (42 to 130)	97 (52.5 to 131)		
Anti-HPV-16, CD4-d-CD40L, S-, Month 7 [N=72,54]	3529.5 (1673 to 6384)	3392 (1692 to 4760)		
Anti-HPV-16, CD4-d-CD40L, S+, Day 0 [N=10,17]	52 (38 to 161)	61 (40 to 164)		
Anti-HPV-16, CD4-d-CD40L, S+, Month 7 [N=10,16]	4852 (1490 to 6368)	1581.5 (1087 to 2193.5)		
Anti-HPV-16, CD4-d-IFNγ, S-, Day 0 [N=86,72]	43 (19 to 67)	43.5 (20 to 73)		
Anti-HPV-16, CD4-d-IFNγ, S-, Month 7 [N=74,54]	823.5 (475 to 1488)	684 (474 to 1185)		
Anti-HPV-16, CD4-d-IFNγ, S+, Day 0 [N=10,17]	37 (22 to 51)	49 (30 to 58)		
Anti-HPV-16, CD4-d-IFNγ, S+, Month 7 [N=10,16]	778 (425 to 2351)	408.5 (270 to 863)		
Anti-HPV-16, CD4-d-IL-2, S-, Day 0 [N=86,72]	58.5 (33 to 98)	86.5 (43.5 to 135.5)		
Anti-HPV-16, CD4-d-IL-2, S-, Month 7 [N=72,54]	3794 (1709 to 6736.5)	3347 (1788 to 5010)		
Anti-HPV-16, CD4-d-IL-2, S+, Day 0 [N=10,17]	53 (24 to 147)	72 (39 to 151)		
Anti-HPV-16, CD4-d-IL-2, S+, Month 7 [N=10,16]	4807.5 (1450 to 6164)	1549 (1145 to 2436.5)		
Anti-HPV-16, CD4-d-TNFα, S-, Day 0 [N=86,72]	58 (35 to 93)	68 (31 to 118.5)		
Anti-HPV-16, CD4-d-TNFα, S-, Month 7 [N=72,54]	2431.5 (1238 to 4743.5)	2713.5 (1224 to 3675)		
Anti-HPV-16, CD4-d-TNFα, S+, Day 0 [N=10,17]	47 (35 to 113)	59 (49 to 84)		
Anti-HPV-16, CD4-d-TNFα, S+, Month 7 [N=10,16]	2128.5 (1353 to 3523)	1185 (838 to 1913.5)		
Anti-HPV-16, CD8-all doubles, S-, Day 0 [N=86,72]	11 (11 to 41)	11 (11 to 44)		
Anti-HPV-16, CD8-all doubles, S-, Month 7[N=72,54]	11 (11 to 41)	11 (11 to 37)		
Anti-HPV-16, CD8-all doubles, S+, Day 0 [N=10,17]	11 (11 to 58)	36 (26 to 43)		
Anti-HPV-16, CD8-all doubles, S+, Month 7[N=10,16]	11 (11 to 11)	33.5 (11 to 43.5)		
Anti-HPV-16, CD8-d-CD40L, S-, Day 0 [N=86,72]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-CD40L, S-, Month 7 [N=72,54]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-CD40L, S+, Day 0 [N=10,17]	7 (7 to 7)	7 (7 to 7)		

Anti-HPV-16, CD8-d-CD40L, S+, Month 7 [N=10,16]	7 (7 to 7)	7 (7 to 22)		
Anti-HPV-16, CD8-d-IFNγ, S-, Day 0 [N=86,72]	7 (7 to 32)	7 (7 to 37)		
Anti-HPV-16, CD8-d-IFNγ, S-, Month 7 [N=72,54]	7 (7 to 34.5)	7 (7 to 27)		
Anti-HPV-16, CD8-d-IFNγ, S+, Day 0 [N=10,17]	7 (7 to 54)	32 (22 to 39)		
Anti-HPV-16, CD8-d-IFNγ, S+, Month 7 [N=10,16]	7 (7 to 7)	22 (7 to 35)		
Anti-HPV-16, CD8-d-IL-2, S-, Day 0 [N=86,72]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IL-2, S-, Month 7 [N=72,54]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IL-2, S+, Day 0 [N=10,17]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IL-2, S+, Month 7 [N=10,16]	7 (7 to 7)	7 (7 to 38)		
Anti-HPV-16, CD8-d-TNFα, S-, Day 0 [N=86,72]	7 (7 to 29)	7 (7 to 28.5)		
Anti-HPV-16, CD8-d-TNFα, S-, Month 7 [N=72,54]	7 (7 to 33)	7 (7 to 32)		
Anti-HPV-16, CD8-d-TNFα, S+, Day 0 [N=10,17]	7 (7 to 54)	22 (7 to 32)		
Anti-HPV-16, CD8-d-TNFα, S+, Month 7 [N=10,16]	7 (7 to 7)	25 (7 to 38)		
Anti-HPV-16, CD4 all doubles, S-, Mth 12 [N=87,74]	2510 (1374 to 5495)	2360.5 (1234 to 3463)		
Anti-HPV-16, CD4 all doubles, S+, Mth 12 [N=11,16]	3317 (1003 to 3428)	1344.5 (874 to 3222.5)		
Anti-HPV-16, CD4-d-CD40L, S-, Mth 12 [N=87,74]	2465 (1310 to 5324)	2316.5 (1218 to 3440)		
Anti-HPV-16, CD4-d-CD40L, S+, Mth 12 [N=11,16]	3287 (975 to 3378)	1334.5 (850 to 3118.5)		
Anti-HPV-16, CD4-d-IFNγ, S-, Mth 12 [N=87,74]	526 (181 to 999)	369 (207 to 718)		
Anti-HPV-16, CD4-d-IFNγ, S+, Mth 12 [N=11,16]	527 (162 to 827)	365.5 (199 to 477.5)		
Anti-HPV-16, CD4-d-IL-2, S-, Mth 12 [N=87,74]	2421 (1275 to 5181)	2273 (1164 to 3242)		
Anti-HPV-16, CD4-d-IL-2, S+, Mth 12 [N=11,16]	3068 (877 to 3424)	1236.5 (814.5 to 3166.5)		
Anti-HPV-16, CD4-d-TNFα, S-, Mth 12 [N=87,74]	1874 (812 to 4009)	1743 (933 to 2521)		
Anti-HPV-16, CD4-d-TNFα, S+, Mth 12 [N=11,16]	2200 (875 to 2891)	1126.5 (685 to 2382)		
Anti-HPV-16, CD8 all doubles, S-, Mth 12 [N=87,74]	11 (11 to 41)	35 (11 to 50)		
Anti-HPV-16, CD8 all doubles, S+, Mth 12 [N=11,16]	52 (11 to 105)	29 (11 to 57)		
Anti-HPV-16, CD8-d-CD40L, S-, Mth 12 [N=87,74]	7 (7 to 32)	7 (7 to 37)		
Anti-HPV-16, CD8-d-CD40L, S+, Mth 12 [N=11,16]	45 (7 to 53)	15 (7 to 36.5)		
Anti-HPV-16, CD8-d-IFNγ, S-, Mth 12 [N=87,74]	7 (7 to 37)	7 (7 to 46)		
Anti-HPV-16, CD8-d-IFNγ, S+, Mth 12 [N=11,16]	46 (7 to 73)	15 (7 to 38)		
Anti-HPV-16, CD8-d-IL-2, S-, Mth 12 [N=87,74]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IL-2, S+, Mth 12 [N=11,16]	7 (7 to 47)	7 (7 to 15)		

Anti-HPV-16, CD8-d-TNFα, S-, Mth 12 [N=87,74]	7 (7 to 39)	7 (7 to 36)		
Anti-HPV-16, CD8-d-TNFα, S+, Mth 12 [N=11,16]	8 (7 to 55)	15 (7 to 29)		
Anti-HPV-16, CD4 all doubles, S-, Month24[N=80,70]	2698 (1217.5 to 5155)	2404.5 (1231 to 3641)		
Anti-HPV-16, CD4 all doubles, S+, Month24[N=10,14]	2979 (1156 to 5489)	1368.5 (1019 to 2390)		
Anti-HPV-16, CD4-d-CD40L, S-, Month 24 [N=80,70]	2443 (1096 to 4946.5)	2347.5 (1096 to 3323)		
Anti-HPV-16, CD4-d-CD40L, S+, Month24 [N=10,14]	2863.5 (945 to 5382)	1217 (795 to 1720)		
Anti-HPV-16, CD4-d-IFNγ, S-, Month 24 [N=80,70]	625 (277.5 to 1312.5)	451 (211 to 884)		
Anti-HPV-16, CD4-d-IFNγ, S+, Month 24 [N=10,14]	686 (398 to 1471)	346.5 (222 to 527)		
Anti-HPV-16, CD4-d-IL-2, S-, Month 24 [N=80,70]	2477 (1133.5 to 4734)	2292.5 (1168 to 3392)		
Anti-HPV-16, CD4-d-IL-2, S+, Month 24 [N=10,14]	2858 (1026 to 5294)	1157 (846 to 1998)		
Anti-HPV-16, CD4-d-TNFα, S-, Month 24 [N=80,70]	2181.5 (878 to 4279.5)	1973 (816 to 2758)		
Anti-HPV-16, CD4-d-TNFα, S+, Month 24 [N=10,14]	2009 (1039 to 4190)	1061.5 (867 to 1867)		
Anti-HPV-16, CD8-all doubles, S-, Month24[N=80,70]	11 (11 to 53)	11 (11 to 54)		
Anti-HPV-16, CD8-all doubles, S+, Month24[N=10,14]	49.5 (12 to 63)	11 (11 to 31)		
Anti-HPV-16, CD8-d-CD40L, S-, Month 24 [N=80,70]	7 (7 to 7)	7 (7 to 31)		
Anti-HPV-16, CD8-d-CD40L, S+, Month 24 [N=10,14]	7 (7 to 46)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IFNγ, S-, Month 24 [N=80,70]	7 (7 to 37.5)	7 (7 to 42)		
Anti-HPV-16, CD8-d-IFNγ, S+, Month 24 [N=10,14]	7.5 (7 to 46)	7 (7 to 19)		
Anti-HPV-16, CD8-d-IL-2, S-, Month 24 [N=80,70]	7 (7 to 30)	7 (7 to 30)		
Anti-HPV-16, CD8-d-IL-2, S+, Month 24 [N=10,14]	7 (7 to 48)	7 (7 to 7)		
Anti-HPV-16, CD8-d-TNFα, S-, Month 24[N=80,70]	7 (7 to 34.5)	7 (7 to 24)		
Anti-HPV-16, CD8-d-TNFα, S+, Month 24[N=10,14]	24.5 (7 to 45)	7 (7 to 7)		
Anti-HPV-16, CD4 all doubles, S-, Month36[N=75,57]	1951 (1085 to 5130)	2073 (1012 to 2836)		
Anti-HPV-16, CD4 all doubles, S+, Month36[N=7,12]	2180 (1293 to 3383)	1310 (939 to 2614.5)		
Anti-HPV-16, CD4-d-CD40L, S-, Month 36 [N=75,57]	1935 (1048 to 5061)	2027 (978 to 2806)		
Anti-HPV-16, CD4-d-CD40L, S+, Month36 [N=7,12]	2109 (1178 to 3343)	1279 (928 to 2496.5)		
Anti-HPV-16, CD4-d-IFNγ, S-, Month 36 [N=75,57]	562 (273 to 1334)	391 (215 to 824)		
Anti-HPV-16, CD4-d-IFNγ, S+, Month 36 [N=7,12]	651 (520 to 998)	564 (185.5 to 714.5)		
Anti-HPV-16, CD4-d-IL-2, S-, Month 36 [N=75,57]	1881 (958 to 4912)	1922 (892 to 2708)		
Anti-HPV-16, CD4-d-IL-2, S+, Month 36 [N=7,12]	2135 (1221 to 3291)	1243 (910.5 to 2382.5)		
Anti-HPV-16, CD4-d-TNFα, S-, Month 36 [N=75,57]	1595 (700 to 3836)	1390 (672 to 2092)		

Anti-HPV-16, CD4-d-TNFα, S+, Month 36 [N=7,12]	1138 (1031 to 2506)	1057 (732 to 2009)		
Anti-HPV-16, CD8-all doubles, S-, Month36[N=75,57]	37 (11 to 72)	35 (11 to 59)		
Anti-HPV-16, CD8-all doubles, S+, Month36[N=7,12]	27 (11 to 123)	11 (11 to 49)		
Anti-HPV-16, CD8-d-CD40L, S-, Month 36 [N=75,57]	11 (7 to 52)	7 (7 to 32)		
Anti-HPV-16, CD8-d-CD40L, S+, Month 36 [N=7,12]	7 (7 to 27)	7 (7 to 15)		
Anti-HPV-16, CD8-d-IFNγ, S-, Month 36 [N=75,57]	11 (7 to 44)	25 (7 to 44)		
Anti-HPV-16, CD8-d-IFNγ, S+, Month 36 [N=7,12]	7 (7 to 63)	7 (7 to 45)		
Anti-HPV-16, CD8-d-IL-2, S-, Month 36 [N=75,57]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-16, CD8-d-IL-2, S+, Month 36 [N=7,12]	7 (7 to 23)	7 (7 to 7)		
Anti-HPV-16, CD8-d-TNFα, S-, Month 36[N=75,57]	7 (7 to 36)	7 (7 to 32)		
Anti-HPV-16, CD8-d-TNFα, S+, Month 36[N=7,12]	7 (7 to 119)	7 (7 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-18 specific T cell-mediated immune response (CMI)

End point title	Cell-mediated immunogenicity related to anti-HPV-18 specific T cell-mediated immune response (CMI)[14]

End point description:

The CMI response was the measure of the cytokines production [IL-2, IFN-γ, TNF-α and CD40L] by HPV-antigen specific T lymphocytes and measured by intracellular cytokine staining (ICS) assay for HPV-18. The frequency was presented as number of cytokine-producing CD4+/CD8+ cells per million CD4+/CD8+ cells. All doubles= T cell expressing at least 2 cytokines. Results were tabulated by the pre-vaccination status of the subjects, where S- = seronegative subjects (antibody titer lower than the cut-off value of 7 EL.U/mL) prior to vaccination. S+ = seropositive subjects (antibody titer ≥ 7 EL.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	80		
Units: cells/million T cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-18, CD4 all doubles, S-, Day 0 [N=83,74]	88 (58 to 129)	109.5 (75 to 175)		

Anti-HPV-18, CD4 all doubles, S-, Month 7[N=69,58]	2629 (1606 to 4256)	1875.5 (1147 to 2565)		
Anti-HPV-18, CD4 all doubles, S+, Day 0 [N=12,16]	112.5 (66.5 to 213)	128 (61.5 to 183)		
Anti-HPV-18, CD4 all doubles, S+, Month 7[N=12,13]	1839 (828 to 3433)	1286 (667 to 2504)		
Anti-HPV-18, CD4-d-CD40L, S-, Day 0 [N=83,74]	59 (35 to 105)	87.5 (56 to 420)		
Anti-HPV-18, CD4-d-CD40L, S-, Month 7 [N=69,58]	2408 (1331 to 3721)	1709.5 (949 to 2324)		
Anti-HPV-18, CD4-d-CD40L, S+, Day 0 [N=12,16]	102 (47.5 to 203)	110.5 (39.5 to 169.5)		
Anti-HPV-18, CD4-d-CD40L, S+, Month 7 [N=12,13]	1719.5 (750.5 to 3203.5)	1232 (614 to 2211)		
Anti-HPV-18, CD4-d-IFNγ, S-, Day 0 [N=83,74]	32 (19 to 55)	33.5 (19 to 70)		
Anti-HPV-18, CD4-d-IFNγ, S-, Month 7 [N=69,58]	558 (220 to 952)	362.5 (192 to 554)		
Anti-HPV-18, CD4-d-IFNγ, S+, Day 0 [N=12,16]	50.5 (13 to 69)	28 (19 to 51.5)		
Anti-HPV-18, CD4-d-IFNγ, S+, Month 7 [N=12,13]	523 (188 to 963.5)	312 (191 to 533)		
Anti-HPV-18, CD4-d-IL-2, S-, Day 0 [N=83,74]	58 (22 to 96)	73 (41 to 125)		
Anti-HPV-18, CD4-d-IL-2, S-, Month 7[N=69,58]	2465 (1452 to 3904)	1760 (1026 to 2329)		
Anti-HPV-18, CD4-d-IL-2, S+, Day 0 [N=12,16]	68 (34.5 to 129)	96.5 (46.5 to 140.5)		
Anti-HPV-18, CD4-d-IL-2, S+, Month 7[N=12,13]	1704 (763.5 to 3223)	1220 (572 to 2282)		
Anti-HPV-18, CD4-d-TNFα, S-, Day 0 [N=83,74]	53 (30 to 72)	73 (29 to 127)		
Anti-HPV-18, CD4-d-TNFα, S-, Month 7 [N=69,58]	1602 (979 to 2822)	1384 (824 to 2030)		
Anti-HPV-18, CD4-d-TNFα, S+, Day 0 [N=12,16]	56 (44.5 to 150.5)	68 (32.5 to 123)		
Anti-HPV-18, CD4-d-TNFα, S+, Month 7 [N=12,13]	1362 (516.5 to 2634.5)	945 (498 to 2050)		
Anti-HPV-18, CD8-all doubles, S-, Day 0 [N=83,74]	11 (11 to 36)	11 (11 to 33)		
Anti-HPV-18, CD8-all doubles, S-, Month 7[N=69,58]	11 (11 to 37)	11 (11 to 32)		
Anti-HPV-18, CD8-all doubles, S+, Day 0 [N=12,16]	11 (11 to 19)	11 (11 to 34.5)		
Anti-HPV-18, CD8-all doubles, S+, Month 7[N=12,13]	11 (11 to 61.5)	11 (11 to 73)		
Anti-HPV-18, CD8-d-CD40L, S-, Day 0 [N=83,74]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-CD40L, S-, Month 7 [N=69,58]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-CD40L, S+, Day 0 [N=12,16]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-CD40L, S+, Month 7 [N=12,13]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IFNγ, S-, Day 0 [N=83,74]	7 (7 to 29)	7 (7 to 24)		
Anti-HPV-18, CD8-d-IFNγ, S-, Month 7 [N=69,58]	7 (7 to 26)	7 (7 to 9)		
Anti-HPV-18, CD8-d-IFNγ, S+, Day 0 [N=12,16]	7 (7 to 15)	7 (7 to 30.5)		
Anti-HPV-18, CD8-d-IFNγ, S+, Month 7 [N=12,13]	7 (7 to 57.5)	7 (7 to 39)		

Anti-HPV-18, CD8-d-IL-2, S-, Day 0 [N=83,74]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IL-2, S-, Month 7 [N=69,58]	7 (7 to 7)	7 (7 to 22)		
Anti-HPV-18, CD8-d-IL-2, S+, Day 0 [N=12,16]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IL-2, S+, Month 7 [N=12,13]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-TNFα, S-, Day 0 [N=83,74]	7 (7 to 12)	7 (7 to 8)		
Anti-HPV-18, CD8-d-TNFα, S-, Month 7 [N=69,58]	7 (7 to 30)	7 (7 to 27)		
Anti-HPV-18, CD8-d-TNFα, S+, Day 0 [N=12,16]	7 (7 to 15)	7 (7 to 30.5)		
Anti-HPV-18, CD8-d-TNFα, S+, Month 7 [N=12,14]	7 (7 to 57.5)	7 (7 to 62)		
Anti-HPV-18, CD4 all doubles, S-, Mth 12 [N=69,58]	2007 (1053 to 3437)	1269 (816 to 2360)		
Anti-HPV-18, CD4 all doubles, S+, Mth 12 [N=12,13]	890 (576 to 2069)	764 (424 to 1771)		
Anti-HPV-18, CD4-d-CD40L, S-, Mth 12 [N=69,58]	1956 (1019 to 3206)	1208 (808 to 2321)		
Anti-HPV-18, CD4-d-CD40L, S+, Mth 12 [N=12,13]	850 (572 to 2008)	752 (402 to 1724)		
Anti-HPV-18, CD4-d-IFNγ, S-, Mth 12 [N=69,58]	340 (132 to 640)	225 (115 to 407)		
Anti-HPV-18, CD4-d-IFNγ, S+, Mth 12 [N=12,13]	239 (102 to 535)	153.5 (85 to 344)		
Anti-HPV-18, CD4-d-IL-2, S-, Mth 12[N=69,58]	1839 (1009 to 3262)	1195 (756 to 2177)		
Anti-HPV-18, CD4-d-IL-2, S+, Mth 12 [N=12,13]	868 (556 to 2022)	744.5 (318 to 1650)		
Anti-HPV-18, CD4-d-TNFα, S-, Mth 12 [N=69,58]	1569 (715 to 2608)	1010 (603 to 1707)		
Anti-HPV-18, CD4-d-TNFα, S+, Mth 12 [N=12,14]	635 (391 to 1696)	632 (372 to 1284)		
Anti-HPV-18, CD8 all doubles, S-, Mth 12 [N=69,58]	13 (11 to 46)	33 (11 to 50)		
Anti-HPV-18, CD8 all doubles, S+, Mth 12 [N=12,13]	47 (11 to 73)	11 (11 to 44)		
Anti-HPV-18, CD8-d-CD40L, S-, Mth 12 [N=69,58]	7 (7 to 32)	7 (7 to 36)		
Anti-HPV-18, CD8-d-CD40L, S+, Mth 12 [N=12,13]	32 (7 to 48)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IFNγ, S-, Mth 12 [N=69,58]	7 (7 to 32)	7 (7 to 38)		
Anti-HPV-18, CD8-d-IFNγ, S+, Mth 12 [N=12,13]	25 (7 to 57)	7 (7 to 36)		
Anti-HPV-18, CD8-d-IL-2, S-, Mth 12[N=69,58]	7 (7 to 25)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IL-2, S+, Mth 12 [N=12,13]	7 (7 to 25)	7 (7 to 23)		
Anti-HPV-18, CD8-d-TNFα, S-, Mth 12 [N=69,58]	7 (7 to 31)	7 (7 to 35)		
Anti-HPV-18, CD8-d-TNFα, S+, Mth 12 [N=12,14]	7 (7 to 55)	7 (7 to 15)		
Anti-HPV-18, CD4 all doubles, S-, Month24[N=79,72]	1784 (874 to 3235)	1355 (650.5 to 2106)		
Anti-HPV-18, CD4 all doubles, S+, Month24[N=10,13]	710.5 (523 to 2329)	777 (467 to 2002)		
Anti-HPV-18, CD4-d-CD40L, S-, Month 24 [N=79,72]	1571 (743 to 3189)	1263 (600.5 to 1883)		

Anti-HPV-18, CD4-d-CD40L, S+, Month24 [N=10,13]	652 (475 to 2151)	745 (394 to 1738)		
Anti-HPV-18, CD4-d-IFNγ, S-, Month 24 [N=79,72]	304 (165 to 773)	210.5 (112 to 519)		
Anti-HPV-18, CD4-d-IFNγ, S+, Month 24 [N=10,13]	295.5 (108 to 636)	160 (92 to 440)		
Anti-HPV-18, CD4-d-IL-2, S-, Month 24 [N=79,72]	1636 (834 to 3092)	1302.5 (602.5 to 1977.5)		
Anti-HPV-18, CD4-d-IL-2, S+, Month 24 [N=10,13]	652.5 (448 to 2269)	652 (395 to 1998)		
Anti-HPV-18, CD4-d-TNFα, S-, Month 24 [N=79,72]	1427 (552 to 2492)	1074.5 (457.5 to 1580)		
Anti-HPV-18, CD4-d-TNFα, S+, Month 24 [N=10,13]	601 (462 to 2122)	702 (360 to 1497)		
Anti-HPV-18, CD8-all doubles, S-, Month24[N=79,72]	11 (11 to 50)	11 (11 to 43)		
Anti-HPV-18, CD8-all doubles, S+, Month24[N=10,13]	19.5 (11 to 47)	11 (11 to 30)		
Anti-HPV-18, CD8-d-CD40L, S-, Month 24 [N=79,72]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-CD40L, S+, Month 24 [N=10,13]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IFNγ, S-, Month 24 [N=79,72]	7 (7 to 29)	7 (7 to 33.5)		
Anti-HPV-18, CD8-d-IFNγ, S+, Month 24 [N=10,13]	7 (7 to 9)	7 (7 to 26)		
Anti-HPV-18, CD8-d-IL-2, S-, Month 24 [N=79,72]	7 (7 to 24)	7 (7 to 14.5)		
Anti-HPV-18, CD8-d-IL-2, S+, Month 24 [N=10,13]	7 (7 to 24)	7 (7 to 7)		
Anti-HPV-18, CD4-d-TNFα, S-, Month 24[N=79,72]	7 (7 to 32)	7 (7 to 33)		
Anti-HPV-18, CD4-d-TNFα, S+, Month 24[N=10,13]	7 (7 to 31)	7 (7 to 7)		
Anti-HPV-18, CD4 all doubles, S-, Month36[N=72,56]	1609 (716 to 3322)	1246 (676.5 to 1751)		
Anti-HPV-18, CD4 all doubles, S+, Month36[N=10,13]	808.5 (624 to 1764)	598 (367 to 1414)		
Anti-HPV-18, CD4-d-CD40L, S-, Month 36 [N=72,56]	1543 (686 to 3258)	1222 (670 to 1665)		
Anti-HPV-18, CD4-d-CD40L, S+, Month36 [N=10,13]	794 (604 to 1721)	594 (350 to 1356)		
Anti-HPV-18, CD4-d-IFNγ, S-, Month 36 [N=72,56]	304.5 (168.5 to 757)	233.5 (114.5 to 485.5)		
Anti-HPV-18, CD4-d-IFNγ, S+, Month 36 [N=10,13]	356 (278 to 417)	239 (102 to 422)		
Anti-HPV-18, CD4-d-IL-2, S-, Month 36 [N=72,56]	1495 (661 to 3065)	1183.5 (586.5 to 1684.5)		
Anti-HPV-18, CD4-d-IL-2, S+, Month 36 [N=10,13]	777 (589 to 1669)	554 (333 to 1370)		
Anti-HPV-18, CD4-d-TNFα, S-, Month 36 [N=72,56]	1268 (473.5 to 2130)	868.5 (520 to 1296.5)		
Anti-HPV-18, CD4-d-TNFα, S+, Month 36 [N=10,13]	652.5 (489 to 1590)	444 (294 to 996)		
Anti-HPV-18, CD8-all doubles, S-, Month36[N=72,56]	32 (11 to 45.5)	29 (11 to 51)		
Anti-HPV-18, CD8-all doubles, S+, Month36[N=10,13]	45 (11 to 85)	34 (11 to 50)		
Anti-HPV-18, CD8-d-CD40L, S-, Month 36 [N=72,56]	7 (7 to 35.5)	7 (7 to 37.5)		
Anti-HPV-18, CD8-d-CD40L, S+, Month 36 [N=10,13]	25 (7 to 61)	7 (7 to 30)		

Anti-HPV-18, CD8-d-IFNγ, S-, Month 36 [N=72,56]	7 (7 to 40.5)	7 (7 to 34.5)		
Anti-HPV-18, CD8-d-IFNγ, S+, Month 36 [N=10,13]	7 (7 to 39)	7 (7 to 40)		
Anti-HPV-18, CD8-d-IL-2, S-, Month 36 [N=72,56]	7 (7 to 7)	7 (7 to 7)		
Anti-HPV-18, CD8-d-IL-2, S+, Month 36 [N=10,13]	7 (7 to 39)	7 (7 to 7)		
Anti-HPV-18, CD8-d-TNFα, S-, Month 36[N=72,56]	7 (7 to 32)	7 (7 to 35)		
Anti-HPV-18, CD8-d-TNFα, S+, Month 36[N=10,13]	17 (7 to 57)	7 (7 to 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-16 specific T cell-mediated immune response (CMI)

End point title	Cell-mediated immunogenicity related to anti-HPV-16 specific T cell-mediated immune response (CMI)[15]

End point description:

The CMI response was the measure of the cytokines production [i.e.interleukin-2 (IL-2), interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α) and cluster of differentiation 40 Ligand (CD40L)] by HPV-antigen specific T lymphocytes and measured by intracellular cytokine staining (ICS) assay for HPV-16 The frequency was presented as number of of cytokine-positive cluster of differentiation (CD)4 i.e.CD4+/CD8+ cells per million CD4+/CD8+ cells. All doubles= T cell expressing at least 2 cytokines. Results were tabulated by the pre-vaccination status of the subjects, where S- = seronegative subjects (antibody titre lower than the cut-off value of 8 EL.U/mL) prior to vaccination. S+ = seropositive subjects (antibody titre ≥ 8 El.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: cells/million T cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-16, CD4 all doubles, S-, Month 0 [N=83]	96 (61 to 170)			
Anti-HPV-16, CD4 all doubles, S-, Month 13 [N=79]	2399 (1514 to 4361)			
Anti-HPV-16, CD4 all doubles, S+, Month 0 [N=7]	169 (77 to 277)			
Anti-HPV-16, CD4 all doubles, S+, Month 13 [N=6]	2507.5 (1067 to 4212)			
Anti-HPV-16, CD4-d-CD40L, S-, Month 0 [N=83]	89 (47 to 133)			

Anti-HPV-16, CD4-d-CD40L, S-, Month 13 [N=79]	2356 (1510 to 4322)			
Anti-HPV-16, CD4-d-CD40L, S+, Month 0 [N=7]	141 (73 to 261)			
Anti-HPV-16, CD4-d-CD40L, S+, Month 13 [N=6]	2450.5 (1036 to 4139)			
Anti-HPV-16, CD4-d-IFNγ, S-, Month 0 [N=83]	37 (20 to 60)			
Anti-HPV-16, CD4-d-IFNγ, S-, Month 13 [N=79]	661 (292 to 1452)			
Anti-HPV-16, CD4-d-IFNγ, S+, Month 0 [N=7]	68 (33 to 203)			
Anti-HPV-16, CD4-d-IFNγ, S+, Month 13 [N=6]	644 (204 to 1163)			
Anti-HPV-16, CD4-d-IL-2, S-, Month 0 [N=83]	63 (34 to 112)			
Anti-HPV-16, CD4-d-IL-2, S-, Month 13 [N=79]	2220 (1406 to 4128)			
Anti-HPV-16, CD4-d-IL-2, S+, Month 0 [N=7]	121 (47 to 191)			
Anti-HPV-16, CD4-d-IL-2, S+, Month 13 [N=6]	2442 (835 to 4006)			
Anti-HPV-16, CD4-d-TNFα, S-, Month 0 [N=83]	63 (36 to 102)			
Anti-HPV-16, CD4-d-TNFα, S-, Month 13 [N=79]	1643 (907 to 3076)			
Anti-HPV-16, CD4-d-TNFα, S+, Month 0 [N=7]	140 (32 to 164)			
Anti-HPV-16, CD4-d-TNFα, S+, Month 13 [N=6]	1843 (584 to 2657)			
Anti-HPV-16, CD8-all doubles, S-, Month 0 [N=83]	31 (11 to 55)			
Anti-HPV-16, CD8-all doubles, S-, Month 13 [N=79]	11 (11 to 43)			
Anti-HPV-16, CD8-all doubles, S+, Month 0 [N=7]	33 (11 to 59)			
Anti-HPV-16, CD8-all doubles, S+, Month 13 [N=6]	43 (11 to 57)			
Anti-HPV-16, CD8-d-CD40L, S-, Month 0 [N=83]	7 (7 to 35)			
Anti-HPV-16, CD8-d-CD40L, S-, Month 13 [N=79]	7 (7 to 30)			
Anti-HPV-16, CD8-d-CD40L, S+, Month 0 [N=7]	7 (7 to 35)			
Anti-HPV-16, CD8-d-CD40L, S+, Month 13 [N=6]	7 (7 to 34)			
Anti-HPV-16, CD8-d-IFNγ, S-, Month 0 [N=83]	23 (7 to 48)			
Anti-HPV-16, CD8-d-IFNγ, S-, Month 13 [N=79]	7 (7 to 35)			
Anti-HPV-16, CD8-d-IFNγ, S+, Month 0 [N=7]	29 (7 to 55)			
Anti-HPV-16, CD8-d-IFNγ, S+, Month 13 [N=6]	25.5 (7 to 53)			
Anti-HPV-16, CD8-d-IL-2, S-, Month 0 [N=83]	7 (7 to 7)			
Anti-HPV-16, CD8-d-IL-2, S-, Month 13 [N=79]	7 (7 to 7)			
Anti-HPV-16, CD8-d-IL-2, S+, Month 0 [N=7]	7 (7 to 7)			
Anti-HPV-16, CD8-d-IL-2, S+, Month 13 [N=6]	7 (7 to 7)			

Anti-HPV-16, CD8-d-TNFα, S-, Month 0 [N=83]	7 (7 to 27)			
Anti-HPV-16, CD8-d-TNFα, S-, Month 13 [N=79]	7 (7 to 29)			
Anti-HPV-16, CD8-d-TNFα, S+, Month 0 [N=7]	7 (7 to 7)			
Anti-HPV-16, CD8-d-TNFα, S+, Month 13 [N=6]	20.5 (7 to 44)			
Anti-HPV-16, CD4 all doubles, S-, Month18 [N=79]	1879 (1102 to 3449)			
Anti-HPV-16, CD4 all doubles, S+, Month18 [N=5]	2299 (1597 to 4103)			
Anti-HPV-16, CD4-d-CD40L, S-, Month 18 [N=79]	1831 (1048 to 3272)			
Anti-HPV-16, CD4-d-CD40L, S+, Month18 [N=5]	2180 (1580 to 3862)			
Anti-HPV-16, CD4-d-IFNγ, S-, Month18 [N=79]	396 (200 to 821)			
Anti-HPV-16, CD4-d-IFNγ, S+, Month 18 [N=5]	685 (361 to 732)			
Anti-HPV-16, CD4-d-IL-2, S-, Month 18 [N=79]	1830 (1023 to 3221)			
Anti-HPV-16, CD4-d-IL-2, S+, Month 18 [N=5]	2249 (1510 to 3870)			
Anti-HPV-16, CD4-d-TNFα, S-, Month 18 [N=79]	1326 (772 to 2627)			
Anti-HPV-16, CD4-d-TNFα, S+, Month 18 [N=5]	1792 (1380 to 2700)			
Anti-HPV-16, CD8-all doubles, S-, Month18 [N=79]	11 (11 to 53)			
Anti-HPV-16, CD8-all doubles, S+, Month18 [N=5]	43 (11 to 52)			
Anti-HPV-16, CD8-d-CD40L, S-, Month 18 [N=79]	7 (7 to 30)			
Anti-HPV-16, CD8-d-CD40L, S+, Month 18 [N=5]	7 (7 to 7)			
Anti-HPV-16, CD8-d-IFNγ, S-, Month 18 [N=79]	7 (7 to 37)			
Anti-HPV-16, CD8-d-IFNγ, S+, Month 18 [N=5]	7 (7 to 33)			
Anti-HPV-16, CD8-d-IL-2, S-, Month 18 [N=79]	7 (7 to 28)			
Anti-HPV-16, CD8-d-IL-2, S+, Month 18 [N=5]	7 (7 to 7)			
Anti-HPV-16, CD8-d-TNFα, S-, Month 18 [N=79]	7 (7 to 41)			
Anti-HPV-16, CD8-d-TNFα, S+, Month 18 [N=5]	33 (7 to 39)			
Anti-HPV-16, CD4 all doubles, S-, Month36 [N=70]	1786.5 (1064 to 3285)			
Anti-HPV-16, CD4 all doubles, S+, Month36 [N=7]	1521 (297 to 3794)			
Anti-HPV-16, CD4-d-CD40L, S-, Month 36 [N=70]	1763 (1048 to 3239)			
Anti-HPV-16, CD4-d-CD40L, S+, Month36 [N=7]	1426 (280 to 3697)			
Anti-HPV-16, CD4-d-IFNγ, S-, Month 36 [N=70]	646 (276 to 1282)			
Anti-HPV-16, CD4-d-IFNγ, S+, Month 36 [N=7]	310 (72 to 1783)			
Anti-HPV-16, CD4-d-IL-2, S-, Month 36 [N=70]	1670.5 (1009 to 3169)			

Anti-HPV-16, CD4-d-IL-2, S+, Month 36 [N=7]	1028 (267 to 3629)			
Anti-HPV-16, CD4-d-TNFα, S-, Month 36 [N=70]	1300.5 (693 to 2267)			
Anti-HPV-16, CD4-d-TNFα, S+, Month 36 [N=7]	1202 (169 to 2745)			
Anti-HPV-16, CD8-all doubles, S-, Month36 [N=70]	21.5 (11 to 52)			
Anti-HPV-16, CD8-all doubles, S+, Month36 [N=7]	11 (11 to 89)			
Anti-HPV-16, CD8-d-CD40L, S-, Month 36 [N=70]	7 (7 to 30)			
Anti-HPV-16, CD8-d-CD40L, S+, Month 36 [N=7]	7 (7 to 46)			
Anti-HPV-16, CD8-d-IFNγ, S-, Month 36 [N=70]	7 (7 to 38)			
Anti-HPV-16, CD8-d-IFNγ, S+, Month 36 [N=7]	7 (7 to 46)			
Anti-HPV-16, CD8-d-IL-2, S-, Month 36 [N=70]	7 (7 to 7)			
Anti-HPV-16, CD8-d-IL-2, S+, Month 36 [N=7]	7 (7 to 46)			
Anti-HPV-16, CD8-d-TNFα, S-, Month 36 [N=70]	7 (7 to 38)			
Anti-HPV-16, CD8-d-TNFα, S+, Month 36 [N=7]	7 (7 to 7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-18 specific T cell-mediated immune response (CMI)

End point title	Cell-mediated immunogenicity related to anti-HPV-18 specific T cell-mediated immune response (CMI)[16]

End point description:

The CMI response was the measure of the cytokines production [IL-2, IFN-γ, TNF-α and CD40L] by HPV-antigen specific T lymphocytes and measured by intracellular cytokine staining (ICS) assay for HPV-18. The frequency was presented as number of cytokine-producing CD4+/CD8+ cells per million CD4+/CD8+ cells. All doubles= T cell expressing at least 2 cytokines. Results were tabulated by the pre-vaccination status of the subjects, where S- = seronegative subjects (antibody titre lower than the cut-off value of 7 EL.U/mL) prior to vaccination. S+ = seropositive subjects (antibody titre ≥ 7 EL.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: cells/million T-cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-18, CD4 all doubles, S-, Month 0 [N=88]	99 (60 to 147)			
Anti-HPV-18, CD4 all doubles, S-, Month 13 [N=83]	1582 (1033 to 3107)			
Anti-HPV-18, CD4 all doubles, S+, Month 0 [N=2]	107.5 (69 to 146)			
Anti-HPV-18, CD4 all doubles, S+, Month 13 [N=2]	1968.5 (1753 to 2184)			
Anti-HPV-18, CD4-d-CD40L, S-, Month 0 [N=88]	85 (41.5 to 126)			
Anti-HPV-18, CD4-d-CD40L, S-, Month 13 [N=83]	1529 (1003 to 3036)			
Anti-HPV-18, CD4-d-CD40L, S+, Month 0 [N=2]	103.5 (65 to 142)			
Anti-HPV-18, CD4-d-CD40L, S+, Month 13 [N=2]	1904.5 (1656 to 2153)			
Anti-HPV-18, CD4-d-IFNγ, S-, Month 0 [N=88]	36 (27 to 61)			
Anti-HPV-18, CD4-d-IFNγ, S-, Month 13 [N=83]	349 (173 to 1221)			
Anti-HPV-18, CD4-d-IFNγ, S+, Month 0 [N=2]	33.5 (24 to 43)			
Anti-HPV-18, CD4-d-IFNγ, S+, Month 13 [N=2]	378 (307 to 449)			
Anti-HPV-18, CD4-d-IL-2, S-, Month 0 [N=88]	60 (32 to 97)			
Anti-HPV-18, CD4-d-IL-2, S-, Month 13 [N=83]	1452 (812 to 2851)			
Anti-HPV-18, CD4-d-IL-2, S+, Month 0 [N=2]	46.5 (33 to 60)			
Anti-HPV-18, CD4-d-IL-2, S+, Month 13 [N=2]	1845 (1544 to 2146)			
Anti-HPV-18, CD4-d-TNFα, S-, Month 0 [N=88]	60 (34 to 97)			
Anti-HPV-18, CD4-d-TNFα, S-, Month 13 [N=83]	1126 (649 to 2076)			
Anti-HPV-18, CD4-d-TNFα, S+, Month 0 [N=2]	66.5 (29 to 104)			
Anti-HPV-18, CD4-d-TNFα, S+, Month 13 [N=2]	1449.5 (1317 to 1582)			
Anti-HPV-18, CD8-all doubles, S-, Month 0 [N=88]	11 (11 to 47.5)			
Anti-HPV-18, CD8-all doubles, S-, Month 13 [N=83]	32 (11 to 53)			
Anti-HPV-18, CD8-all doubles, S+, Month 0 [N=2]	29 (11 to 47)			
Anti-HPV-18, CD8-all doubles, S+, Month 13 [N=2]	63.5 (39 to 88)			
Anti-HPV-18, CD8-d-CD40L, S-, Month 0 [N=88]	7 (7 to 31)			
Anti-HPV-18, CD8-d-CD40L, S-, Month 13 [N=83]	7 (7 to 38)			
Anti-HPV-18, CD8-d-CD40L, S+, Month 0 [N=2]	25 (7 to 43)			

Anti-HPV-18, CD8-d-CD40L, S+, Month 13 [N=2]	21 (7 to 35)			
Anti-HPV-18, CD8-d-IFNγ, S-, Month 0 [N=88]	7 (7 to 41.5)			
Anti-HPV-18, CD8-d-IFNγ, S-, Month 13 [N=83]	7 (7 to 44)			
Anti-HPV-18, CD8-d-IFNγ, S+, Month 0 [N=2]	25 (7 to 43)			
Anti-HPV-18, CD8-d-IFNγ, S+, Month 13 [N=2]	59.5 (35 to 84)			
Anti-HPV-18, CD8-d-IL-2, S-, Month 0 [N=88]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IL-2, S-, Month 13 [N=83]	7 (7 to 19)			
Anti-HPV-18, CD8-d-IL-2, S+, Month 0 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IL-2, S+, Month 13 [N=2]	45.5 (7 to 84)			
Anti-HPV-18, CD8-d-TNFα, S-, Month 0 [N=88]	7 (7 to 38)			
Anti-HPV-18, CD8-d-TNFα, S-, Month 13 [N=83]	7 (7 to 31)			
Anti-HPV-18, CD8-d-TNFα, S+, Month 0 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD8-d-TNFα, S+, Month 13 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD4 all doubles, S-, Month18 [N=82]	1165.5 (767 to 2116)			
Anti-HPV-18, CD4 all doubles, S+, Month18 [N=2]	1250 (1156 to 1344)			
Anti-HPV-18, CD4-d-CD40L, S-, Month 18 [N=82]	1140.5 (721 to 2098)			
Anti-HPV-18, CD4-d-CD40L, S+, Month18 [N=2]	1174.5 (1110 to 1239)			
Anti-HPV-18, CD4-d-IFNγ, S-, Month18 [N=82]	224.5 (107 to 572)			
Anti-HPV-18, CD4-d-IFNγ, S+, Month 18 [N=2]	157.5 (136 to 179)			
Anti-HPV-18, CD4-d-IL-2, S-, Month 18 [N=82]	1095 (710 to 1924)			
Anti-HPV-18, CD4-d-IL-2, S+, Month 18 [N=2]	1151 (1078 to 1224)			
Anti-HPV-18, CD4-d-TNFα, S-, Month 18 [N=82]	896.5 (537 to 1783)			
Anti-HPV-18, CD4-d-TNFα, S+, Month 18 [N=2]	954.5 (873 to 1036)			
Anti-HPV-18, CD8-all doubles, S-, Month18 [N=82]	33.5 (11 to 51)			
Anti-HPV-18, CD8-all doubles, S+, Month18 [N=2]	11 (11 to 11)			
Anti-HPV-18, CD8-d-CD40L, S-, Month 18 [N=82]	7 (7 to 34)			
Anti-HPV-18, CD8-d-CD40L, S+, Month 18 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IFNγ, S-, Month 18 [N=82]	7 (7 to 38)			
Anti-HPV-18, CD8-d-IFNγ, S+, Month 18 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IL-2, S-, Month 18 [N=82]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IL-2, S+, Month 18 [N=2]	7 (7 to 7)			

Anti-HPV-18, CD8-d-TNFα, S-, Month 18 [N=82]	7 (7 to 40)			
Anti-HPV-18, CD8-d-TNFα, S+, Month 18 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD4 all doubles, S-, Month36 [N=75]	1158 (606 to 2185)			
Anti-HPV-18, CD4 all doubles, S+, Month36 [N=2]	1399.5 (1004 to 1795)			
Anti-HPV-18, CD4-d-CD40L, S-, Month 36 [N=75]	1154 (563 to 2157)			
Anti-HPV-18, CD4-d-CD40L, S+, Month36 [N=2]	1320 (918 to 1722)			
Anti-HPV-18, CD4-d-IFNγ, S-, Month 36 [N=75]	318 (140 to 766)			
Anti-HPV-18, CD4-d-IFNγ, S+, Month 36 [N=2]	389 (231 to 547)			
Anti-HPV-18, CD4-d-IL-2, S-, Month 36 [N=75]	1086 (535 to 1974)			
Anti-HPV-18, CD4-d-IL-2, S+, Month 36 [N=2]	1160 (827 to 1493)			
Anti-HPV-18, CD4-d-TNFα, S-, Month 36 [N=75]	812 (384 to 1545)			
Anti-HPV-18, CD4-d-TNFα, S+, Month 36 [N=2]	1127 (847 to 1407)			
Anti-HPV-18, CD8-all doubles, S-, Month36 [N=75]	33 (11 to 56)			
Anti-HPV-18, CD8-all doubles, S+, Month36 [N=2]	45 (11 to 79)			
Anti-HPV-18, CD8-d-CD40L, S-, Month 36 [N=75]	7 (7 to 38)			
Anti-HPV-18, CD8-d-CD40L, S+, Month 36 [N=2]	41 (7 to 75)			
Anti-HPV-18, CD8-d-IFNγ, S-, Month 36 [N=75]	7 (7 to 44)			
Anti-HPV-18, CD8-d-IFNγ, S+, Month 36 [N=2]	41 (7 to 75)			
Anti-HPV-18, CD8-d-IL-2, S-, Month 36 [N=75]	7 (7 to 7)			
Anti-HPV-18, CD8-d-IL-2, S+, Month 36 [N=2]	7 (7 to 7)			
Anti-HPV-18, CD8-d-TNFα, S-, Month 36 [N=75]	7 (7 to 35)			
Anti-HPV-18, CD8-d-TNFα, S+, Month 36 [N=2]	7 (7 to 7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-16 specific B cell-mediated immune response

End point title	Cell-mediated immunogenicity related to anti-HPV-16 specific B cell-mediated immune response[17]

End point description:

The cell-mediated immune response was assessed as being the frequency of B-cell memory of HPV-16 antigen-specific memory B-cells per million memory B-cells in subjects with detectable B-cells. The results are presented by pre-vaccination status, where S- = seronegative subjects (antibody concentration < 8 EL.U/mL) prior to vaccination and S+ = seropositive subjects (antibody concentration

≥ 8 EL.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	91		
Units: cells/million B-cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-16, S-, Day 0 [N=79, 69]	1 (1 to 1)	1 (1 to 1)		
Anti-HPV-16, S-, Month 7 [N=75, 55]	2210 (886 to 5171)	1692 (849 to 3449)		
Anti-HPV-16, S-, Month 12 [N=59, 43]	801 (437 to 2553)	1136 (371 to 3215)		
Anti-HPV-16, S+, Day 0 [N=10, 17]	1 (1 to 1)	16 (1 to 58)		
Anti-HPV-16, S+, Month 7 [N=9, 15]	4467 (1513 to 8673)	1354 (197 to 4928)		
Anti-HPV-16, S+, Month 12 [N=3, 10]	5018 (1064 to 5094)	785 (340 to 2517)		
Anti-HPV-16, S-, Month 24 [N=78, 63]	305.5 (93 to 696)	590 (142 to 1130)		
Anti-HPV-16, S+, Month 24 [N=8, 14]	621 (324.5 to 1751.5)	568.5 (22 to 1854)		
Anti-HPV-16, S-, Month 36 [N=70, 53]	560.5 (157 to 1012)	448 (219 to 821)		
Anti-HPV-16, S+, Month 36 [N=6, 13]	475 (414 to 822)	107 (1 to 1275)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-18 specific B cell-mediated immune response

End point title	Cell-mediated immunogenicity related to anti-HPV-18 specific B cell-mediated immune response[18]

End point description:

The cell-mediated immune response was assessed as being the frequency of B-cell memory of HPV-18 antigen-specific memory B-cells per million memory B-cells in subjects with detectable B-cells. The results are presented by pre-vaccination status, where S- = seronegative subjects (antibody concentration < 7 EL.U/mL) prior to vaccination and S+ = seropositive subjects (antibody concentration ≥ 7 EL.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Day 0 and Months 7, 12, 24 and 36

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 1 Group	Cervarix 2 Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	92		
Units: cells/million B-cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-18, S-, Day 0 [N=78,71]	0 (0 to 0)	0 (0 to 0)		
Anti-HPV-18, S-, Month 7 [N=73,58]	935 (407 to 2485)	838 (430 to 2062)		
Anti-HPV-18, S+, Day 0 [N=11,16]	0 (0 to 85)	0 (0 to 11)		
Anti-HPV-18, S+, Month 7 [N=11,13]	2175 (423 to 3414)	755 (180 to 2505)		
Anti-HPV-18, S-, Month 24 [N=75, 65]	209 (53 to 664)	274 (71 to 829)		
Anti-HPV-18, S+, Month 24 [N=11, 13]	299 (117 to 643)	352 (237 to 952)		
Anti-HPV-18, S-, Month 36 [N=67,54]	269 (62 to 732)	284.5 (90 to 582)		
Anti-HPV-18, S+, Month 36 [N=9,12]	154 (141 to 427)	93 (18 to 762)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-16 specific B cell-mediated immune response

End point title	Cell-mediated immunogenicity related to anti-HPV-16 specific B cell-mediated immune response[19]

End point description:

The cell-mediated immune response was assessed as being the frequency of B-cell memory of HPV-16 antigen-specific memory B-cells per million memory B-cells in subjects with detectable B-cells. The results are presented by pre-vaccination status, where S- = seronegative subjects (antibody concentration < 8 EL.U/mL) prior to vaccination and S+ = seropositive subjects (antibody concentration ≥ 8 EL.U/mL) prior to vaccination.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: cells/million T-cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-16, S-, Month 0 [N=71]	1 (1 to 7)			
Anti-HPV-16, S-, Month 13 [N=72]	2825 (1429.5 to 5421)			
Anti-HPV-16, S+, Month 0 [N=5]	1 (1 to 20)			
Anti-HPV-16, S+, Month 13 [N=5]	5996 (919 to 7353)			
Anti-HPV-16, S-, Month 18 [N=65]	769 (418 to 1825)			
Anti-HPV-16, S+, Month 18 [N=4]	1469 (454 to 2520.5)			
Anti-HPV-16, S-, Month 36 [N=67]	613 (322 to 1301)			
Anti-HPV-16, S+, Month 36 [N=6]	425 (102 to 714)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cell-mediated immunogenicity related to anti-HPV-18 specific B cell-mediated immune response

End point title	Cell-mediated immunogenicity related to anti-HPV-18 specific B cell-mediated immune response[20]

End point description:

The cell-mediated immune response was assessed as being the frequency of B-cell memory of HPV-18 antigen-specific memory B-cells per million memory B-cells in subjects with detectable B-cells. The results are presented by pre-vaccination status, where S- = seronegative subjects (antibody concentration < 7 EL.U/mL) prior to vaccination and S+ = seropositive subjects (antibody concentration ≥ 7 EL.U/mL) prior to vaccination. Note: Results for Months 18, 24 and 36 will be updated when they become available. For this group, results were only made available one month after the last vaccine dose, at Month 13.

End point type	Secondary

End point timeframe:

At Months 0, 13, 18, 24 and 36

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As Group Cervarix 3 received the last vaccination dose at Month 12, results were presented separately for Groups Cervarix 3 and for Cervarix 1 and 2.

End point values	Cervarix 3 Group			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: cells/million B-cells				
median (inter-quartile range (Q1-Q3))				
Anti-HPV-18, S-, Month 0 [N=75]	0 (0 to 0)			

Anti-HPV-18, S-, Month 13 [N=75]	1165 (632 to 1780)			
Anti-HPV-18, S+, Month 0 [N=1]	48 (48 to 48)			
Anti-HPV-18, S+, Month 13 [N=2]	758 (114 to 1402)			
Anti-HPV-18, S-, Month 18 [N=68]	561.5 (132 to 1142)			
Anti-HPV-18, S+, Month 18 [N=1]	938 (938 to 938)			
Anti-HPV-18, S-, Month 36 [N=72]	361 (112 to 724)			
Anti-HPV-18, S+, Month 36 [N=1]	1231 (1231 to 1231)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms were collected during the 7-day period (Days 0-6) after vaccination.Unsolicited AEs were collected during the 30-day period (Days 0-29) after vaccination. SAEs were collected from Day 0 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	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Cervarix 1 Group

Reporting group description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 6. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Reporting group title	Cervarix 3 Group

Reporting group description:

Female subjects aged 9 to 14 years at the time of the first vaccination, who received 2 doses of the Cervarix vaccine at Months 0 and 12. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Reporting group title	Cervarix 2 Group

Reporting group description:

Female subjects aged 15 to 25 years at the time of the first vaccination, who received 3 doses of the Cervarix vaccine at Months 0, 1 and 6. The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Serious adverse events	Cervarix 1 Group	Cervarix 3 Group	Cervarix 2 Group
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 550 (3.64%)	24 / 415 (5.78%)	28 / 482 (5.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Medulloblastoma			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholesteatoma			

subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Synovial sarcoma			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
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			
Circulatory collapse			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Surgical and medical procedures			
Ectopic pregnancy termination			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Hyperemesis gravidarum			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Premature baby			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abortion threatened			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Postpartum haemorrhage			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stillbirth			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Anaphylactic reaction			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Transient tachypnoea of the newborn			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			

subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Psychiatric disorders			
Schizoaffective disorder			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	2 / 482 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizoaffective disorder [14]	Additional description: [14] up to Month 13		
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Forearm fracture			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Carbon monoxide poisoning			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Intentional overdose			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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

Ligament rupture			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol poisoning			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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			
Convulsion			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Seizure			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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	1 / 550 (0.18%)	1 / 415 (0.24%)	0 / 482 (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
Eye disorders			
Strabismus			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Gastrointestinal disorders			
Abdominal strangulated hernia			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Abdominal pain			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Abdominal pain lower			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Anal haemorrhage			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Constipation			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Dyspepsia			

subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Faecaloma			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Gastritis			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Nausea			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Pelvic inflammatory disease			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Renal and urinary disorders			

IgA nephropathy			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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			
Synovial cyst			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Infections and infestations			
Dengue fever			
subjects affected / exposed	1 / 550 (0.18%)	3 / 415 (0.72%)	3 / 482 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 550 (0.36%)	2 / 415 (0.48%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Acute tonsillitis			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Tonsillitis			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Appendicitis			
subjects affected / exposed	0 / 550 (0.00%)	2 / 415 (0.48%)	2 / 482 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious mononucleosis			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Peritonitis			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
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	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis [1]	Additional description: [1] up to Month 36		
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Pelvic infection			
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Viral infection			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Appendicitis [2]	Additional description: [2] up to Month 13		
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	0 / 482 (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
Appendicitis [3]	Additional description: [3] up to Month 36		

subjects affected / exposed	0 / 550 (0.00%)	5 / 415 (1.20%)	3 / 482 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever [4]	Additional description: [4] up to Month 36		
subjects affected / exposed	1 / 550 (0.18%)	3 / 415 (0.72%)	4 / 482 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis [5]	Additional description: [5] up to Month 36		
subjects affected / exposed	0 / 550 (0.00%)	2 / 415 (0.48%)	0 / 482 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza [6]	Additional description: [6] up to Month 36		
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis [7]	Additional description: [7] up to Month 36		
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever [8]	Additional description: [8] up to Month 13		
subjects affected / exposed	1 / 550 (0.18%)	1 / 415 (0.24%)	3 / 482 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis [9]	Additional description: [9] up to Month 13		
subjects affected / exposed	1 / 550 (0.18%)	1 / 415 (0.24%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever [10]	Additional description: [10] SAEs for Cervarix 3 Group were assessed only after the last vaccination at Month 12.		
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	2 / 482 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis [11]	Additional description: [11] SAEs for Cervarix 3 Group were assessed only after the last vaccination at Month 12.		

subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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 bacterial [12]	Additional description: [12] SAEs for Cervarix 3 Group were assessed only after the last vaccination at Month 12.		
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	0 / 550 (0.00%)	1 / 415 (0.24%)	1 / 482 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 550 (0.18%)	0 / 415 (0.00%)	0 / 482 (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
Hypovolaemia [13]	Additional description: [13] up to Month 13		
subjects affected / exposed	0 / 550 (0.00%)	0 / 415 (0.00%)	1 / 482 (0.21%)
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 1 Group	Cervarix 3 Group	Cervarix 2 Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	499 / 550 (90.73%)	381 / 415 (91.81%)	461 / 482 (95.64%)
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	499 / 550 (90.73%)	381 / 415 (91.81%)	461 / 482 (95.64%)
occurrences (all)	499	381	461
Redness			
alternative assessment type: Systematic			

subjects affected / exposed	247 / 550 (44.91%)	197 / 415 (47.47%)	212 / 482 (43.98%)
occurrences (all)	247	197	212
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	225 / 550 (40.91%)	171 / 415 (41.20%)	204 / 482 (42.32%)
occurrences (all)	225	171	204
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	111 / 550 (20.18%)	93 / 415 (22.41%)	107 / 482 (22.20%)
occurrences (all)	111	93	107
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	247 / 550 (44.91%)	215 / 415 (51.81%)	310 / 482 (64.32%)
occurrences (all)	247	215	310
Gastrointestinal symptoms			
alternative assessment type: Systematic			
subjects affected / exposed	98 / 550 (17.82%)	77 / 415 (18.55%)	134 / 482 (27.80%)
occurrences (all)	98	77	134
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	204 / 550 (37.09%)	185 / 415 (44.58%)	246 / 482 (51.04%)
occurrences (all)	204	185	246
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	278 / 550 (50.55%)	221 / 415 (53.25%)	295 / 482 (61.20%)
occurrences (all)	278	221	295
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	41 / 550 (7.45%)	42 / 415 (10.12%)	48 / 482 (9.96%)
occurrences (all)	41	42	48
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	22 / 550 (4.00%) 22	14 / 415 (3.37%) 14	27 / 482 (5.60%) 27

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	The HPV-070 protocol is being amended for the following reason: The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported