



## Clinical trial results:

**A phase III, double-blind, randomized, controlled study to evaluate the safety, immunogenicity and efficacy of GlaxoSmithKline Biologicals' HPV 16/18 L1/AS04 vaccine administered intramuscularly according to a three-dose schedule (0, 1, 6 month) in healthy adult female subjects aged 26 years and above.**

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

## Summary

EudraCT number	2005-002546-20
Trial protocol	GB PT
Global end of trial date	29 January 2014

## Results information

Result version number	v2
This version publication date	27 April 2016
First version publication date	15 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Data for secondary endpoints have been added. Data correction due to a system error in EudraCT – Results.

## Trial information

### Trial identification

Sponsor protocol code	104820
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00294047
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	No

1901/2006 apply to this trial?
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Notes:

## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	19 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

-To demonstrate efficacy of the candidate vaccine in the prevention of (1) persistent infection (6-month definition) with HPV-16 or HPV-18 (by polymerase chain reaction [PCR]) and/or (2) histopathologically confirmed CIN1+ associated with HPV-16 or HPV-18 cervical infection detected within the lesional component of the cervical tissue specimen (by PCR) (combined endpoint), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by enzyme-linked immunosorbent assay [ELISA]).

If efficacy is demonstrated, the following objective will be assessed sequentially:

-To demonstrate efficacy of the candidate vaccine in the prevention of (1) persistent infection (6-month definition) with HPV-16 or HPV-18 (by PCR) and/or (2) histopathologically-confirmed CIN1+ associated with HPV-16 or HPV-18 cervical infection detected using the HPV TAA, overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

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 vaccinee remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 February 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	84 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 195
Country: Number of subjects enrolled	Canada: 422
Country: Number of subjects enrolled	Mexico: 1298
Country: Number of subjects enrolled	Netherlands: 361
Country: Number of subjects enrolled	Peru: 178
Country: Number of subjects enrolled	Philippines: 738

Country: Number of subjects enrolled	Portugal: 212
Country: Number of subjects enrolled	Russian Federation: 300
Country: Number of subjects enrolled	Singapore: 234
Country: Number of subjects enrolled	Thailand: 500
Country: Number of subjects enrolled	United Kingdom: 272
Country: Number of subjects enrolled	United States: 1072
Worldwide total number of subjects	5782
EEA total number of subjects	845

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5782
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Some subjects completed the study at Month 36 since they did not want to participate to the one-year extension up to Month 48. The number of subjects who participated up to Month 48 in the Cervarix Group = 2305 (80.0%) and in the Aluminium Hydroxide Group = 2281 (79.4%).

### Pre-assignment

Screening details:

Enrolment was stratified by (1) age, with the majority of subjects in age strata 26 – 35 years and 36 – 45 years (about 45% each) and about 10% in the age stratum 46+ years, and (2) previous HPV history (in each age stratum, the number of women with a history of HPV infection/treatment was limited to approximately 15%).

### Pre-assignment period milestones

Number of subjects started	5782
Number of subjects completed	5752

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	No vaccination received: 30
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### Period 1

Period 1 title	Month 48 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Cervarix Group
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Arm description:

Subjects received 3 doses of Cervarix™ vaccine. Cervarix vaccine was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.

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 were planned to receive three doses of the study vaccine administered intramuscularly according to a 0, 1, 6 month vaccination schedule.

<b>Arm title</b>	Aluminium Hydroxide Group
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Arm description:

Subjects received 3 doses of Aluminium Hydroxide [Al(OH)<sub>3</sub>]. Aluminium Hydroxide was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.

Arm type	Placebo Comparator
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Investigational medicinal product name	Placebo control
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects were planned to receive three doses of the control vaccine administered intramuscularly according to a 0, 1, 6 month vaccination schedule.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Cervarix Group	Aluminium Hydroxide Group
Started	2881	2871
Completed	2456	2438
Not completed	425	433
Consent withdrawn by subject	111	115
Adverse event, non-fatal	28	13
Unspecified	10	14
Lost to follow-up	272	287
Protocol deviation	4	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of the 5782 subjects enrolled in the study, not all received the study vaccination, hence only 5752 started.

## Baseline characteristics

### Reporting groups

Reporting group title	Cervarix Group
Reporting group description:	
Subjects received 3 doses of Cervarix™ vaccine. Cervarix vaccine was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.	
Reporting group title	Aluminium Hydroxide Group
Reporting group description:	
Subjects received 3 doses of Aluminium Hydroxide [Al(OH) <sub>3</sub> ]. Aluminium Hydroxide was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.	

Reporting group values	Cervarix Group	Aluminium Hydroxide Group	Total
Number of subjects	2881	2871	5752
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	37	37	
standard deviation	± 7.24	± 7.32	-
Gender categorical Units: Subjects			
Female	2881	2871	5752
Male	0	0	0

## End points

### End points reporting groups

Reporting group title	Cervarix Group
Reporting group description:	
Subjects received 3 doses of Cervarix™ vaccine. Cervarix vaccine was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.	
Reporting group title	Aluminium Hydroxide Group
Reporting group description:	
Subjects received 3 doses of Aluminium Hydroxide [Al(OH)3]. Aluminium Hydroxide was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.	

### Primary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection.

End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection. <sup>[1]</sup>
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#### End point description:

CIN1+ = CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Persistent HPV infection = detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. - DNA- and sero-/+ : subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and 6 and seronegative/positive (sero-/+ ) at Month 0 for the corresponding HPV-type by Enzyme-linked Immunosorbent Assay (ELISA) - Overall: subjects DNA- at Month 0 and 6 for the corresponding HPV-type, regardless of initial serostatus

End point type	Primary
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#### End point timeframe:

Up to Month 48

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N= 1898;1854)	7	36		
HPV-16, DNA- and sero- subjects (N=1545;1521)	5	27		
HPV-18, DNA- and sero- subjects (N=1597;1571)	2	10		
HPV-16/18, DNA- and sero+ subjects (N=900;864)	2	14		
HPV-16, DNA- and sero+ subjects (N=605;594)	1	9		
HPV-18, DNA- and sero+ subjects (N=574;550)	1	5		

HPV-16/18, overall (N=2224;2190)	9	51		
HPV-16, overall (N=2167;2131)	6	36		
HPV-18, overall (N=2203;2165)	3	16		

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA). <sup>[2]</sup>
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End point description:

CIN1+ = CIN grades 1, 2 and 3, AIS and invasive cervical cancer. Persistent cervical HPV infection (6-month definition) = detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. - DNA- and sero-/+ : subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Primary
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End point timeframe:

Up to Month 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1898;1854)	7	36		
HPV-16, DNA- and sero- subjects (N=1545;1521)	5	27		
HPV-18, DNA- and sero- subjects (N=1597;1571)	2	10		
HPV-16/18, DNA- and sero+ subjects (N=900;864)	2	12		
HPV-16, DNA- and sero+ subjects (N=605;594)	1	8		
HPV-18, DNA- and sero+ subjects (N=574;550)	1	4		
HPV-16/18, overall (N=2224;2190)	9	49		
HPV-16, overall (N=2167;2131)	6	35		
HPV-18, overall (N=2203;2165)	3	15		



## Statistical analyses

No statistical analyses for this end point

### **Primary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN) 1+ associated with HPV-16 and/or -18 cervical infection.**

End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN) 1+ associated with HPV-16 and/or -18 cervical infection. <sup>[3]</sup>
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#### End point description:

CIN1+ = CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Persistent HPV infection = detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. - DNA- and sero-/+ : subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and 6 and seronegative/positive (sero-/+ ) at Month 0 for the corresponding HPV-type by Enzyme-linked Immunosorbent Assay (ELISA) - Overall: subjects DNA- at Month 0 and 6 for the corresponding HPV-type, regardless of initial serostatus.

End point type	Primary
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#### End point timeframe:

Up to Month 84

#### Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2168	2147		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N= 1852;1818)	7	71		
HPV-16, DNA- and sero- subjects (N=1507;1491)	5	53		
HPV-18, DNA- and sero- subjects (N=1565;1541)	3	20		
HPV-16/18, DNA- and sero+ subjects (N=870;849)	3	16		
HPV-16, DNA- and sero+ subjects (N=588;584)	2	10		
HPV-18, DNA- and sero+ subjects (N=552;540)	1	6		
HPV-16/18, overall (N=2168;2147)	10	90		
HPV-16, overall (N=2112;2091)	7	63		
HPV-18, overall (N=2149;2123)	4	29		

## Statistical analyses

No statistical analyses for this end point

### **Primary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).**

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA). <sup>[4]</sup>
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End point description:

CIN1+ = CIN grades 1, 2 and 3, AIS and invasive cervical cancer. Persistent cervical HPV infection (6-month definition) = detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. - DNA- and sero-/+ : subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Primary
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End point timeframe:

Up to Month 84

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2168	2147		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1852;1818)	7	71		
HPV-16, DNA- and sero- subjects (N=1507;1491)	5	53		
HPV-18, DNA- and sero- subjects (N=1565;1541)	2	20		
HPV-16/18, DNA- and sero+ subjects (N=870;849)	3	14		
HPV-16, DNA- and sero+ subjects (N=588;584)	2	9		
HPV-18, DNA- and sero+ subjects (N=552;540)	1	5		
HPV-16/18, overall (N=2168;2147)	10	88		
HPV-16, overall (N=2112;2091)	7	62		
HPV-18, overall (N=2149;2123)	3	28		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18

End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done in: - DNA- and sero-/+: subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2178	2152		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1859;1822)	6	34		
HPV-16, DNA- and sero- subjects (N=1518;1495)	5	26		
HPV-18, DNA- and sero- subjects (N=1566;1542)	1	8		
HPV-16/18, DNA- and sero+ subjects (N=880;851)	2	11		
HPV-16, DNA- and sero+ subjects (N=591;583)	1	8		
HPV-18, DNA- and sero+ subjects (N=562;543)	1	3		
HPV-16/18, overall (N=2178;2152)	8	45		
HPV-16, overall (N=2126;2094)	6	34		
HPV-18, overall (N=2160;2127)	2	11		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of subjects with persistent infection (12-month definition) with human papillomavirus (HPV)-16 or HPV-18**

End point title	Number of subjects with persistent infection (12-month definition) with human papillomavirus (HPV)-16 or HPV-18
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## End point description:

Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type(s) PCR in cervical samples at all available time points over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals). - DNA- and sero-/+ : subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary
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## End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2146	2124		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1832;1800)	2	18		
HPV-16, DNA- and sero- subjects (N=1499;1476)	1	12		
HPV-18, DNA- and sero- subjects (N=1543;1525)	1	6		
HPV-16/18, DNA- and sero+ subjects (N=864;839)	0	3		
HPV-16, DNA- and sero+ subjects (N=579;577)	0	2		
HPV-18, DNA- and sero+ subjects (N=553;532)	0	1		
HPV-16/18, overall (N=2146;2124)	2	21		
HPV-16, overall (N=2095;2069)	1	14		
HPV-18, overall (N=2128;2099)	1	7		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects with persistent infection (6-month Definition) with oncogenic HPV types individually or in combinations.**

End point title	Number of subjects with persistent infection (6-month Definition) with oncogenic HPV types individually or in combinations.
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## End point description:

Persistent cervical HPV infection (6-month definition) = detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects HPV DNA- for the corresponding HPV type at baseline (at month 0 and Month 6) regardless of initial serostatus. HPV-HRW=All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18. HPV-HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2179	2154		
Units: Subjects				
HPV-16 (N=2126;2094)	6	34		
HPV-18 (N=2160;2127)	2	11		
HPV-31 (N=2126;2132)	4	19		
HPV-33 (N=2158;2136)	8	6		
HPV-35 (N=2165;2144)	8	13		
HPV-39 (N=2150;2119)	20	11		
HPV-45 (N=2160;2130)	4	17		
HPV-51 (N=2125;2113)	27	26		
HPV-52 (N=2113;2101)	33	38		
HPV-56 (N=2154;2123)	16	20		
HPV-58 (N=2152;2135)	12	8		
HPV-59 (N=2158;2126)	12	11		
HPV-66 (N=2141;2122)	27	27		
HPV-68 (N=2138;2128)	15	23		
HPV-31/45 (N=2175;2152)	8	35		
HPV-31/45/33/52/58 (N=2179;2154)	58	83		
HPV-39/45/59/68 (N=2179;2154)	50	60		
HPV-31/33/35/52/58 (N=2179;2154)	63	80		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2179;2154)	132	146		
HPV-HRW (N=2179;2154)	163	185		
HPV-HR (N=2179;2154)	170	217		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with persistent infection (12-month Definition) with oncogenic HPV types individually or in combinations.

End point title	Number of subjects with persistent infection (12-month Definition) with oncogenic HPV types individually or in combinations.
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End point description:

Persistent HPV infection (12-month definition) = detection of the same HPV type(s) by PCR in cervical samples at available time points over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals). Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. subjects HPV DNA- for the corresponding HPV type at Month 0 6, regardless of initial serostatus. HPV-HRW=All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HPV-HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 , 68

End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2147	2126		
Units: Subjects				
HPV-16 (N=2095;2069)	1	14		
HPV-18 (N=2128;2099)	1	7		
HPV-31 (N=2096;2104)	2	10		
HPV-33 (N=2126;2110)	5	5		
HPV-35 (N=2133;2116)	3	8		
HPV-39 (N=2119;2091)	12	5		
HPV-45 (N=2129;2102)	4	8		
HPV-51 (N=2093;2086)	11	14		
HPV-52 (N=2081;2074)	21	23		
HPV-56 (N=2124;2096)	4	8		
HPV-58 (N=2120;2108)	8	7		
HPV-59 (N=2126;2098)	4	3		
HPV-66 (N=2109;2094)	10	8		
HPV-68 (N=2106;2100)	7	13		
HPV-31/45 (N=2144;2124)	6	17		
HPV-31/45/33/52/58 (N=2147;2126)	39	49		
HPV-39/45/59/68 (N=2147;2126)	27	29		
HPV-31/33/35/52/58 (N=2147;2126)	38	51		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2147;2126)	70	84		
HPV-HRW (N=2147;2126)	86	105		
HPV-HR (N=2147;2126)	88	122		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen
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End point description:

CIN2+ was defined as CIN grades 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in: - DNA- and sero-: subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

Note: Results for seropositive status were not analysed.

End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1898;1854)	0	4		
HPV-16, DNA- and sero- subjects (N=1545;1521)	0	3		
HPV-18, DNA- and sero- subjects (N=1597;1571)	0	2		
HPV-16/18, overall (N=2224;2190)	0	6		
HPV-16, overall (N=2167;2131)	0	3		
HPV-18, overall (N=2203;2165)	0	4		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in: - DNA- and sero-/+ : subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1898;1854)	1	7		
HPV-16, DNA- and sero- subjects (N=1545;1521)	0	5		
HPV-18, DNA- and sero- subjects (N=1597;1571)	1	3		
HPV-16/18, DNA- and sero+ subjects (N=900;864)	0	3		
HPV-16, DNA- and sero+ subjects (N=605;594)	0	1		
HPV-18, DNA- and sero+ subjects (N=574;550)	0	2		
HPV-16/18, overall (N=2224;2190)	1	11		
HPV-16, overall (N=2167;2131)	0	6		
HPV-18, overall (N=2203;2165)	1	6		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2740	2737		
Units: Subjects				
HPV-16/18	35	56		
HPV-16	24	42		
HPV-18	13	20		



## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ irrespective of HPV cervical infection and irrespective of baseline HPV DNA status

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ irrespective of HPV cervical infection and irrespective of baseline HPV DNA status
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA status.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2740	2737		
Units: Subjects				
CIN1+	152	178		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any cytological abnormalities associated with HPV-16 or HPV-18 cervical infection

End point title	Number of subjects with any cytological abnormalities associated with HPV-16 or HPV-18 cervical infection
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End point description:

Cytological abnormalities = atypical squamous cells of undetermined significance (ASC-US). Detection was done in: - DNA- and sero-: subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline. Results for seropositive status were not analysed.

End point type	Secondary
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End point timeframe:

Up to Month 48

<b>End point values</b>	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1898;1854)	2	31		
HPV-16, DNA- and sero- subjects (N=1545;1521)	2	24		
HPV-18, DNA- and sero- subjects (N=1597;1571)	0	8		
HPV-16/18, overall (N=2224;2190)	5	38		
HPV-16 (N=2167;2131)	4	27		
HPV-18 (N=2203;2165)	1	12		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with cytological abnormalities associated with oncogenic HPV types individually or in combinations

End point title	Number of subjects with cytological abnormalities associated with oncogenic HPV types individually or in combinations
End point description:	
Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative for the corresponding HPV type at baseline (at month 0 and Month 6) regardless of initial serostatus. HRW-HPV= All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HPV-HR= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68	
End point type	Secondary
End point timeframe:	
Up to Month 48	

<b>End point values</b>	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2225	2192		
Units: Subjects				
HPV-16 (N=2167;2131)	4	27		
HPV-18 (N=2203;2165)	1	12		
HPV-31 (N=2172;2170)	4	12		
HPV-33 (N=2204;2173)	4	4		
HPV-35 (N=2211;2181)	4	10		
HPV-39 (N=2196;2156)	10	11		

HPV-45 (N=2206;2168)	3	17		
HPV-51 (N=2171;2149)	21	18		
HPV-52 (N=2158;2139)	19	19		
HPV-56 (N=2200;2158)	9	19		
HPV-58 (N=2198;2172)	12	6		
HPV-59 (N=2202;2164)	4	15		
HPV-66 (N=2187;2160)	13	26		
HPV-68 (N=2184;2164)	8	8		
HPV-31/45 (N=2221;2190)	7	28		
HPV-31/45/33/52/58 (N=2225;2192)	40	54		
HPV-39/45/59/68 (N=2225;2192)	24	48		
HPV-31/33/35/52/58 (N=2225;2192)	41	49		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2225;2192)	79	107		
HPV-HRW (N=2225;2192)	94	126		
HPV-HR (N=2225;2192)	96	148		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with histopathologically confirmed reduction of local cervical therapy

End point title	Number of subjects with histopathologically confirmed reduction of local cervical therapy
End point description:	
Detection was done on all subjects irrespective of their baseline HPV DNA status.	
End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2740	2737		
Units: Subjects				
Reduction of local cervical therapy	76	84		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with first colposcopy

End point title	Number of subjects with first colposcopy
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End point description:

Detection was done on all subjects irrespective of their baseline HPV DNA status.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2741	2738		
Units: Subjects				
First colposcopy	392	422		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection

End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2772	2779		
Units: Subjects				
HPV-16/18	90	158		
HPV-16	64	118		
HPV-18	30	52		

## Statistical analyses

No statistical analyses for this end point

### **Secondary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-confirmed CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).**

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-confirmed CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus. The lesion was assigned to an HPV type found in the lesion if (1) the same HPV type was found in at least 1 of the 2 (closest) preceding cytology samples, or (2) none of the HPV types found in the lesion were found in any of the 2 preceding cytology samples (isolate HPV types)

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2772	2779		
Units: Subjects				
HPV-16/18	89	155		
HPV-16	63	117		
HPV-18	29	49		

## Statistical analyses

No statistical analyses for this end point

### **Secondary: Number of seroconverted subjects against HPV-16 in the immunogenicity subset.**

End point title	Number of seroconverted subjects against HPV-16 in the immunogenicity subset.
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End point description:

Seroconversion was defined as the appearance of antibodies (i.e.; titre greater than or equal to the cut-

off value) in the serum of subjects seronegative before vaccination. HPV-16 assay cut-off value was defined as greater than or equal to 8 ELISA units per millilitre (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 8 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 8 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites N≥1000, at least 250 per region

End point type	Secondary
End point timeframe:	
At pre-vaccination and at Month 7, 12, 18, 24, 36 and 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	374		
Units: Subjects				
Sero- before vaccination (N=406;374)	0	0		
Sero- at Month 7 (N=406;371)	406	13		
Sero- at Month 12 (N=384;349)	384	28		
Sero- at Month 18 (N=377;340)	377	9		
Sero- at Month 24 (N=392;350)	392	11		
Sero- at Month 36 (N=361;320)	361	23		
Sero- at Month 48 (N=345;316)	345	31		
Sero+ before vaccination (N=170;179)	170	179		
Sero+ at Month 7 (N=170;179)	170	166		
Sero+ at Month 12 (N=154;158)	154	151		
Sero+ at Month 18 (N=147;154)	147	136		
Sero+ at Month 24 (N=158;165)	158	144		
Sero+ at Month 36 (N=137;146)	137	131		
Sero+ at Month 48 (N=132;145)	132	135		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of seroconverted subjects against HPV-18 in the immunogenicity subset.

End point title	Number of seroconverted subjects against HPV-18 in the immunogenicity subset.
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End point description:

Seroconversion was defined as the appearance of antibodies (i.e.; titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination. HPV-18 assay cut-off value was defined as greater than or equal to 7 ELISA units per millilitre (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 7 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 7 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites N≥1000, at least 250 per region

End point type	Secondary
End point timeframe:	
At pre-vaccination and at Month 7, 12, 18, 24, 36 and 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	405	379		
Units: Subjects				
Sero- before vaccination (N=405;379)	0	0		
Sero- at Month 7 (N=405;374)	405	12		
Sero- at Month 12 (N=376;352)	375	16		
Sero- at Month 18 (N=366;347)	366	12		
Sero- at Month 24 (N=389;358)	387	14		
Sero- at Month 36 (N=348;328)	346	14		
Sero- at Month 48 (N=338;320)	336	16		
Sero+ before vaccination (N=163;164)	163	164		
Sero+ at Month 7 (N=163;161)	163	146		
Sero+ at Month 12 (N=154;144)	154	133		
Sero+ at Month 18 (N=149;141)	149	118		
Sero+ at Month 24 (N=153;150)	153	114		
Sero+ at Month 36 (N=142;131)	142	92		
sero+ at Month 48 (N=133;131)	133	94		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean concentrations (GMCs) against HPV-16 antibody in the immunogenicity subset.

End point title	Geometric mean concentrations (GMCs) against HPV-16 antibody in the immunogenicity subset.
End point description:	
GMCs were expressed in ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 7 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 7 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites (N≥1000, at least 250 per region)	
End point type	Secondary
End point timeframe:	
At pre-vaccination and at Month 7, 12, 18, 24, 36 and 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	406	374		
Units: EL.U/mL				
geometric mean (confidence interval)				

95%)				
Sero- before vaccination (N=406;374)	0 (0 to 0)	0 (0 to 0)		
Sero- at Month 7 (N=406;371)	5412.9 (4934.3 to 5938)	4.3 (4.1 to 4.4)		
Sero- at Month 12 (N=384;349)	1542.5 (1393.2 to 1707.8)	4.4 (4.2 to 4.5)		
Sero- at Month 18 (N=377;340)	992.6 (893.9 to 1102.2)	4.1 (4 to 4.2)		
Sero- at Month 24 (N=392;350)	827.8 (745.2 to 919.5)	4.2 (4.1 to 4.4)		
Sero- at Month 36 (N=361;320)	612.9 (550.1 to 682.8)	4.5 (4.2 to 4.7)		
Sero- at Month 48 (N=345;316)	546.2 (490.4 to 608.2)	4.6 (4.4 to 4.9)		
Sero+ before vaccination (N=170;179)	39.3 (33.6 to 45.9)	38.6 (33.2 to 44.9)		
Sero+ at Month 7 (N=170;179)	5845.5 (5113.8 to 6682)	33.4 (28.2 to 39.5)		
Sero+ at month 12 (N=154;158)	2705.8 (2313.2 to 3165.1)	38 (32 to 45.3)		
Sero+ at Month 18 (N=147;154)	2104.7 (1780.5 to 2487.8)	30.5 (25.2 to 36.9)		
Sero+ at Month 24 (N=158;165)	1883.5 (1599.4 to 2218.1)	29.6 (24.5 to 35.7)		
Sero+ at month 36 (N=137;146)	1363.8 (1138.2 to 1634.2)	30.6 (25.3 to 37)		
Sero+ at Month 48 (N=132;145)	1261.2 (1048.4 to 1517.1)	34.3 (28.8 to 40.8)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean concentrations (GMCs) against HPV-18 antibody in the immunogenicity subset.

End point title	Geometric mean concentrations (GMCs) against HPV-18 antibody in the immunogenicity subset.
End point description: GMCs were expressed in ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 7 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 7 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites (N≥1000, at least 250 per region)	
End point type	Secondary
End point timeframe: At pre-vaccination and at Month 7, 12, 18, 24, 36 and 48	



End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	405	379		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Sero- before vaccination (N=405;379)	0 (0 to 0)	0 (0 to 0)		
Sero- at Month 7 (N=405;374)	2567.7 (2339.5 to 2818.2)	3.7 (3.6 to 3.9)		
Sero- at Month 12 (N=376;352)	645.3 (576.6 to 722.1)	3.7 (3.6 to 3.9)		
Sero- at Month 18 (N=366;347)	402.6 (359.7 to 450.6)	3.7 (3.6 to 3.8)		
Sero- at Month 24 (N=389;358)	321.7 (286.9 to 360.7)	3.7 (3.6 to 3.9)		
Sero- at Month 36 (N=348;328)	245.9 (218.5 to 276.8)	3.7 (3.6 to 3.8)		
Sero- at Month 48 (N=338;320)	228.5 (201.9 to 258.7)	3.7 (3.6 to 3.8)		
Sero+ before vaccination (N=163;164)	23 (19.9 to 26.7)	24.2 (20.6 to 28.4)		
Sero+ at Month 7 (N=163;161)	2933.9 (2557.1 to 3366.3)	21.9 (18.1 to 26.5)		
Sero+ at Month 12 (N=154;144)	936.2 (796.4 to 1100.4)	23.6 (19.4 to 28.7)		
Sero+ at Month 18 (N=149;141)	661.3 (560.9 to 779.7)	19.5 (15.7 to 24.2)		
Sero+ at Month 24 (N=153;150)	573.6 (487.7 to 674.6)	16.6 (13.5 to 20.5)		
Sero+ at Month 36 (N=142;131)	423.1 (357.9 to 500.1)	16.4 (12.9 to 20.7)		
Sero+ at Month 48 (N=133;131)	392.3 (328.9 to 468)	15.9 (12.7 to 19.9)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of seroconverted subjects against HPV-16 and HPV-18 viral neutralization in a selected subset of subjects.

End point title	Number of seroconverted subjects against HPV-16 and HPV-18 viral neutralization in a selected subset of subjects.
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End point description:

Seroconversion was defined as the appearance of antibodies (i.e.; titre greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination. HPV-16/18 assay cut-off value was defined as greater than or equal to 40 Estimated dose 50% (ED50). Sero- subjects are subjects who had an antibody concentration below 40 ED50 prior to vaccination. Sero+ subjects are subjects who had an antibody concentration equal to or above 50 ED50 prior to vaccination. ED50 = the estimated serum dilution reducing the signal generated by viral infection by 50%.

End point type	Secondary
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End point timeframe:

Prior to vaccination and at Month 7, 12, 18, 24, 48 and 84.

<b>End point values</b>	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: Subjects				
HPV-16 sero- [pre-vaccination] (N=37;37)	0	0		
HPV-16 sero- [at Month 7] (N=37;37)	37	1		
HPV-16 sero- [at Month 12] (N=37;37)	37	0		
HPV-16 sero- [at Month 18] (N=36;37)	36	0		
HPV-16 sero- [at Month 24] (N=35;37)	35	2		
HPV-16 sero- [at Month 48] (N=27;33)	27	1		
HPV-16 sero+ [pre-vaccination] (N=4;1)	4	1		
HPV-16 sero+ [at Month 7] (N=4;1)	4	1		
HPV-16 sero+ [at Month 12] (N=4;1)	4	1		
HPV-16 sero+ [at Month 18] (N=4;1)	4	1		
HPV-16 sero+ [at Month 24] (N=4;1)	4	0		
HPV-16 sero+ [at Month 48] (N=3;1)	3	0		
HPV-18 sero- [pre-vaccination] (N=38;35)	0	0		
HPV-18 sero- [at Month 7] (N=38;35)	38	0		
HPV-18 sero- [at Month 12] (N=38;35)	38	0		
HPV-18 sero- [at Month 18] (N=37;35)	37	0		
HPV-18 sero- [at Month 24] (N=36;35)	36	1		
HPV-18 sero- [at Month 48] (N=29;32)	29	0		
HPV-18 sero+ [pre-vaccination] (N=3;3)	3	3		
HPV-18 sero+ [at Month 7] (N=3;3)	3	2		
HPV-18 sero+ [at Month 12] (N=3;3)	3	2		
HPV-18 sero+ [at Month 18] (N=3;3)	3	2		
HPV-18 sero+ [at Month 24] (N=3;3)	3	2		
HPV-18 sero+ [at Month 48] (N=1;2)	1	1		
HPV-16 sero- [at Month 84] (N=20;25)	19	1		
HPV-16 sero+ [at Month 84] (N=3;1)	3	1		
HPV-18 sero- [at Month 84] (N=22;25)	22	0		
HPV-18 sero+ [at Month 84] (N=1;1)	1	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean titers (GMTs) against HPV-16 and HPV-18 viral neutralization antibodies in a selected subset of subjects.

End point title	Geometric mean titers (GMTs) against HPV-16 and HPV-18 viral neutralization antibodies in a selected subset of subjects.
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End point description:

Titers are expressed as geometric mean antibody titers (GMTs). Seronegative (Sero-) subjects are subjects who had an antibody titer below 40 ED50 prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody titer equal to or above 40 ED50 prior to vaccination. ED50 = Estimated dose 50%, the estimated serum dilution reducing the signal generated by viral infection by 50%.

End point type	Secondary
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End point timeframe:

Prior to vaccination and at Month 7, 12, 18, 24, 48 and 84.

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: Titers				
geometric mean (confidence interval 95%)				
HPV-16 sero- [pre-vaccination] (N=37;37)	20 (20 to 20)	20 (20 to 20)		
HPV-16 sero- [at Month 7] (N=37;37)	11663.5 (7507.2 to 18120.8)	20.8 (19.2 to 22.4)		
HPV-16 sero- [at Month 12] (N=37;37)	5597.7 (3688.3 to 8495.6)	20 (20 to 20)		
HPV-16 sero- [at Month 18] (N=36;37)	2175.2 (1390.8 to 3401.9)	20 (20 to 20)		
HPV-16 sero- [at Month 24] (N=35;37)	1941.7 (1193 to 3160.4)	22.3 (18.6 to 26.6)		
HPV-16 sero- [at Month 48] (N=27;33)	828.9 (488.4 to 1406.7)	21.4 (18.7 to 24.5)		
HPV-16 sero+ [pre-vaccination] (N=4;1)	139.3 (32.7 to 594.2)	45 (45 to 45)		
HPV-16 sero+ [at Month 7] (N=4;1)	20283.2 (2428.3 to 169422)	107 (107 to 107)		
HPV-16 sero+ [at Month 12] (N=4;1)	19484.3 (7049.3 to 53854.2)	99 (99 to 99)		
HPV-16 sero+ [at Month 18] (N=4;1)	4393.3 (798.4 to 24175)	93 (93 to 93)		
HPV-16 sero+ [at Month 24] (N=4;1)	9459.1 (2168.4 to 41263.7)	20 (20 to 20)		
HPV-16 sero+ [at Month 48] (N=3;1)	4187.2 (676.4 to 25921.6)	20 (20 to 20)		
HPV-18 sero- [pre-vaccination] (N=38;35)	20 (20 to 20)	20 (20 to 20)		
HPV-18 sero- [at Month 7] (N=38;35)	7959.6 (4648 to 13630.7)	20 (20 to 20)		
HPV-18 sero- [at Month 12] (N=38;35)	1979.9 (1201.6 to 3262.5)	20 (20 to 20)		
HPV-18 sero- [at Month 18] (N=37;35)	1334.6 (793.3 to 2245.3)	20 (20 to 20)		

HPV-18 sero- [at Month 24] (N=36;35)	826.6 (493.6 to 1384.1)	21.4 (18.7 to 24.5)		
HPV-18 sero- [at Month 48] (N=29;32)	386.1 (203.9 to 731.1)	20 (20 to 20)		
HPV-18 sero+ [pre-vaccination] (N=3;3)	84.7 (9.2 to 782.4)	115.5 (21.5 to 621)		
HPV-18 sero+ [at Month 7] (N=3;3)	3014.5 (446.3 to 20361.5)	163.4 (0.8 to 31959.2)		
HPV-18 sero+ [at Month 12] (N=3;3)	3377.8 (2563.9 to 4450.1)	167.3 (0.8 to 35164.4)		
HPV-18 sero+ [at Month 18] (N=3;3)	3125.8 (595.8 to 16398.4)	254.9 (0.4 to 172814)		
HPV-18 sero+ [at Month 24] (N=3;3)	2493 (261.2 to 23793.7)	154.9 (0.4 to 53341.9)		
HPV-18 sero+ [at Month 48] (N=1;2)	545 (545 to 545)	86 (0 to 9999)		
HPV-16 sero- [at Month 84] (N=20;25)	1213.4 (529.8 to 2779.1)	22.9 (17.3 to 30.4)		
HPV-16 sero+ [at Month 84] (N=3;1)	5837 (963.7 to 35354.6)	104 (104 to 104)		
HPV-18 sero- [at Month 84] (N=22;25)	491.2 (232.9 to 1036)	20 (20 to 20)		
HPV-18 sero+ [at Month 84] (N=1;1)	532 (532 to 532)	968 (968 to 968)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting any and Grade 3 solicited local symptoms.

End point title	Number of subjects reporting any and Grade 3 solicited local symptoms.
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End point description:

Solicited local symptoms assessed were pain, redness and swelling. Any was defined as any solicited local symptom reported irrespective of intensity. Grade 3 pain was defined as pain that prevented normal activity. Grade 3 redness and swelling was defined as redness/swelling above 50 millimeter (mm).

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0-6) after vaccination

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2830	2831		
Units: Subjects				
Any pain	2411	1862		
Grade 3 pain	303	73		
Any redness	1058	530		
Grade 3 redness	44	5		

Any swelling	1080	428		
Grade 3 swelling	97	11		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting any, Grade 3 and related solicited general symptoms.

End point title	Number of subjects reporting any, Grade 3 and related solicited general symptoms.
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End point description:

Solicited general symptoms assessed were arthralgia, fatigue, gastrointestinal, headache, myalgia, rash, urticaria and fever (Fever = axillary temperature above 37.5 degrees Celsius (°C)). Any = any solicited general symptom reported irrespective of intensity and relationship to vaccination. Related = symptoms considered by the investigator to have a causal relationship to vaccination. Grade 3 symptoms = symptoms that prevented normal activity. Grade 3 urticaria = urticaria distributed on at least 4 body areas. Grade 3 fever = axillary temperature above 39.0°C.

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0-6) after vaccination

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2832	2832		
Units: Subjects				
Any arthralgia	580	439		
Grade3 arthralgia	30	24		
Related arthralgia	323	225		
Any fatigue	1116	916		
Grade 3 fatigue	78	53		
Related fatigue	678	545		
Any fever	308	248		
Grade 3 fever	17	8		
Related fever	181	159		
Any gastrointestinal	664	592		
Grade 3 gastrointestinal	60	54		
Related gastrointestinal	335	312		
Any headache	1165	1074		
Grade 3 headache	76	72		
Related headache	666	598		
Any myalgia	878	622		
Grade 3 myalgia	46	32		
Related myalgia	541	391		
Any rash	185	124		
Grade 3 rash	1	7		

Related rash	88	61		
Any urticaria	258	201		
Grade 3 urticaria	21	18		
Related urticaria	84	79		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting any, Grade 3 and related unsolicited adverse events (AEs).

End point title	Number of subjects reporting any, Grade 3 and related unsolicited adverse events (AEs).
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End point description:

An unsolicited adverse event is any adverse event (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) 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. Grade 3 unsolicited AE = an event that prevented normal activity. A related AE = event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

Within 30 days (Days 0 – 29) post-vaccination period.

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2881	2871		
Units: Subjects				
Any AEs	1154	1164		
Grade 3 AEs	207	184		
Related AEs	246	192		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects reporting any and related serious adverse events (SAEs).

End point title	Number of subjects reporting any and related serious adverse events (SAEs).
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End point description:

SAEs assessed include medical occurrences that results in death, are life threatening, require hospitalization or prolongation of hospitalization, results in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subjects. A related SAE was defined as an event assessed by the investigator as causally related to the study vaccination.

End point type	Secondary
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End point timeframe:

Up to Month 48 and up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2881	2871		
Units: Subjects				
Any SAEs, M48	286	266		
Related SAEs, M48	5	8		
Any SAEs, M84	291	269		
Related SAEs, M84	5	8		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting new onset of chronic disease (NOCDs).

End point title	Number of subjects reporting new onset of chronic disease (NOCDs).
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End point description:

NOCDs include autoimmune disorders, asthma and type I diabetes.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2881	2871		
Units: Subjects				
NOCDs	143	165		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting new onset of autoimmune disease (NOADs).

End point title	Number of subjects reporting new onset of autoimmune disease (NOADs).
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End point description:

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2881	2871		
Units: Subjects				
NOADs	24	24		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting medically significant conditions (MAEs).

End point title	Number of subjects reporting medically significant conditions (MAEs).
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End point description:

Medically significant conditions were defined as: AEs prompting emergency room or physician visits that were not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that were not related to common diseases. Common diseases included: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

End point type	Secondary
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End point timeframe:

Up to Month 48

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2881	2871		
Units: Subjects				
MAEs	1170	1140		

### Statistical analyses

No statistical analyses for this end point



**Secondary: Number of subjects with pregnancies and their outcomes.**

End point title	Number of subjects with pregnancies and their outcomes.
End point description:	
Pregnancy outcomes are live infant, premature live infant, elective termination, ectopic pregnancy, spontaneous abortion, lost to follow-up and pregnancy ongoing. For each category it was specified if the infant presents congenital anomaly (CA) or no apparent congenital anomaly (No ACA).	
End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	357		
Units: Subjects				
Live infant No ACA, M48	259	249		
Live infant CA, M48	4	7		
Elective termination No ACA, M48	19	24		
Elective termination CA, M48	1	0		
Ectopic pregnancy, M48	5	6		
Spontaneous abortion No ACA, M48	69	66		
Spontaneous abortion CA, M48	0	1		
Stillbirth No ACA, M48	0	2		
Lost to follow-up, M48	2	2		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected using the type assignment algorithm (TAA)**

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected using the type assignment algorithm (TAA)
End point description:	
CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline. TAA: Type assignment algorithm. The lesion was assigned to an HPV type found in the lesion if a) the same HPV type was found in at least one of the two (closest) preceding cytology samples, or b) none of the HPV types found in the lesion were found in any of the two preceding cytology samples (isolate HPV types)	
End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2224	2190		
Units: Subjects				
HPV-16/18 DNA- (N=2224;2190)	1	9		
HPV-16 DNA- (N=2167;2131)	0	5		
HPV-18 DNA- (N=2203;2165)	1	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18.

End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18.
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done in: - DNA- and sero-/+ : subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2124	2109		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1815;1786)	6	67		
HPV-16, DNA- and sero- subjects (N=1482;1466)	5	51		
HPV-18, DNA- and sero- subjects (N=1535;1511)	1	17		
HPV-16/18, DNA- and sero+ subjects (N=851;837)	3	13		
HPV-16, DNA- and sero+ subjects (N=574;573)	2	9		
HPV-18, DNA- and sero+ subjects (N=541;534)	1	4		
HPV-16/18, overall (N=2124;2109)	9	82		

HPV-16, overall (N=2073;2055)	7	60		
HPV-18, overall (N=2108;2085)	2	23		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with persistent infection (12-month definition) with human papillomavirus (HPV)-16 or HPV-18.

End point title	Number of subjects with persistent infection (12-month definition) with human papillomavirus (HPV)-16 or HPV-18.
End point description:	
Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type(s) PCR in cervical samples at all available time points over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals). - DNA- and sero-/+: subjects HPV DNA negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+) for HPV-16 and/or HPV-18 by ELISA at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.	
End point type	Secondary
End point timeframe:	
Up to Month 84	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2093	2081		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1789;1764)	2	37		
HPV-16, DNA- and sero- subjects (N=1464;1447)	1	27		
HPV-18, DNA- and sero- subjects (N=1513;1494)	1	10		
HPV-16/18, DNA- and sero+ subjects (N=835;825)	0	5		
HPV-16, DNA- and sero+ subjects (N=562;567)	0	3		
HPV-18, DNA- and sero+ subjects (N=532;523)	0	2		
HPV-16/18, overall (N=2093;2081)	2	43		
HPV-16, overall (N=2043;2030)	1	30		
HPV-18, overall (N=2077;2057)	1	13		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with persistent infection (6-month Definition) with oncogenic HPV types individually or in combinations.

End point title	Number of subjects with persistent infection (6-month Definition) with oncogenic HPV types individually or in combinations.
End point description:	
Persistent cervical HPV infection (6-month definition) = detection of the same HPV type(s) by PCR in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects HPV DNA- for the corresponding HPV type at baseline (at month 0 and Month 6) regardless of initial serostatus. HPV-HRW=All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18. HPV-HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.	
End point type	Secondary
End point timeframe:	
Up to Month 84	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2125	2111		
Units: Subjects				
HPV-16 (N=2073;2055)	7	60		
HPV-18 (N=2108;2085)	2	23		
HPV-31 (N=2073;2090)	10	29		
HPV-33 (N=2105;2094)	12	9		
HPV-35 (N=2112;2101)	11	17		
HPV-39 (N=2097;2078)	34	26		
HPV-45 (N=2106;2088)	9	30		
HPV-51 (N=2071;2072)	48	42		
HPV-52 (N=2060;2058)	54	56		
HPV-56 (N=2100;2081)	28	30		
HPV-58 (N=2098;2092)	24	19		
HPV-59 (N=2105;2083)	22	21		
HPV-66 (N=2089;2080)	45	49		
HPV-68 (N=2084;2085)	31	33		
HPV-31/45 (N=2121;2109)	19	57		
HPV-31/45/33/52/58 (N=2125;2111)	98	128		
HPV-39/45/59/68 (N=2125;2111)	92	102		
HPV-31/33/35/52/58 (N=2125;2111)	101	118		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2125;2111)	206	220		
HPV-HRW (N=2125;2111)	255	274		
HPV-HR (N=2125;2111)	262	330		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with persistent infection (12-month Definition) with oncogenic HPV types individually or in combinations.

End point title	Number of subjects with persistent infection (12-month Definition) with oncogenic HPV types individually or in combinations.
End point description:	
Persistent HPV infection (12-month definition) = detection of the same HPV type(s) by PCR in cervical samples at available time points over approximately a 12-month interval (evaluations are planned at approximately 6-month intervals). Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. subjects HPV DNA- for the corresponding HPV type at Month 0 6, regardless of initial serostatus. HPV-HRW=All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HPV-HR=High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 , 68.	
End point type	Secondary
End point timeframe:	
Up to Month 84	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2094	2083		
Units: Subjects				
HPV-16 (N=2043;2030)	1	30		
HPV-18 (N=2077;2057)	1	13		
HPV-31 (N=2044;2062)	7	17		
HPV-33 (N=2074;2068)	9	7		
HPV-35 (N=2081;2073)	5	9		
HPV-39 (N=2067;2050)	20	10		
HPV-45 (N=2076;2060)	7	13		
HPV-51 (N=2040;2045)	23	26		
HPV-52 (N=2029;2031)	34	31		
HPV-56 (N=2071;2054)	11	15		
HPV-58 (N=2067;2065)	14	13		
HPV-59 (N=2074;2055)	7	10		
HPV-66 (N=2058;2052)	22	16		
HPV-68 (N=2053;2057)	13	22		
HPV-31/45 (N=2091;2081)	14	28		
HPV-31/45/33/52/58 (N=2094;2083)	65	75		
HPV-39/45/59/68 (N=2094;2083)	46	54		
HPV-31/33/35/52/58 (N=2094;2083)	64	72		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2094;2083)	118	129		
HPV-HRW (N=2094;2083)	145	160		
HPV-HR (N=2094;2083)	147	194		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.**

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.
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End point description:

CIN2+ was defined as CIN grades 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in: - DNA- and sero-: subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline. Note: Results for seropositive status were not analyzed.

End point type	Secondary
End point timeframe:	
Up to Month 84	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2168	2146		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1852;1818)	1	6		
HPV-16, DNA- and sero- subjects (N=1507;1491)	1	5		
HPV-18, DNA- and sero- subjects (N=1565;1541)	1	2		
HPV-16/18, overall (N=2168;2146)	1	8		
HPV-16, overall (N=2112;2090)	1	5		
HPV-18, overall (N=2149;2122)	1	4		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.**

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in: - DNA- and sero-/+ : subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative/positive (sero-/+ ) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2168	2146		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1852;1818)	2	12		
HPV-16, DNA- and sero- subjects (N=1507;1491)	1	9		
HPV-18, DNA- and sero- subjects (N=1565;1541)	2	4		
HPV-16/18, DNA- and sero+ subjects (N=870;848)	0	3		
HPV-16, DNA- and sero+ subjects (N=588;583)	0	1		
HPV-18, DNA- and sero+ subjects (N=552;539)	0	2		
HPV-16/18, overall (N=2168;2146)	2	16		
HPV-16, overall (N=2112;2090)	1	10		
HPV-18, overall (N=2149;2122)	2	7		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection detected within the lesional component of the cervical tissue specimen.
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus.

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2733	2735		
Units: Subjects				
HPV-16/18	37	66		
HPV-16	26	49		
HPV-18	14	23		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ irrespective of HPV cervical infection and irrespective of baseline HPV DNA status.

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ irrespective of HPV cervical infection and irrespective of baseline HPV DNA status.
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End point description:

CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA status.

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2733	2735		
Units: Subjects				
Subjects	179	229		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with any cytological abnormalities associated with HPV-16 or HPV-18 cervical infection.

End point title	Number of subjects with any cytological abnormalities associated with HPV-16 or HPV-18 cervical infection.
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End point description:

Cytological abnormalities = atypical squamous cells of undetermined significance (ASC-US). Detection was done in: - DNA- and sero-: subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). - Overall: subjects DNA- at Month



0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline. Results for seropositive status were not analyzed.

End point type	Secondary
End point timeframe:	
Up to Month 84	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2168	2146		
Units: Subjects				
HPV-16/18, DNA- and sero- subjects (N=1852;1818)	3	47		
HPV-16, DNA- and sero- subjects (N=1507;1491)	3	34		
HPV-18, DNA- and sero- subjects (N=1565;1541)	0	14		
HPV-16/18, overall (N=2168;2146)	6	56		
HPV-16 (N=2112;2090)	5	38		
HPV-18 (N=2149;2122)	1	19		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with cytological abnormalities associated with oncogenic HPV types individually or in combinations.

End point title	Number of subjects with cytological abnormalities associated with oncogenic HPV types individually or in combinations.
End point description:	
Oncogenic HPV types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative for the corresponding HPV type at baseline (at month 0 and Month 6) regardless of initial serostatus. HRW-HPV= All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HPV-HR= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 .	
End point type	Secondary
End point timeframe:	
Up to Month 48	

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2169	2146		
Units: Subjects				
HPV-16 (N=2112;2090)	5	38		
HPV-18 (N=2149;2122)	1	19		

HPV-31 (N=2117;2127)	5	23		
HPV-33 (N=2149;2130)	6	8		
HPV-35 (N=2156;2137)	7	13		
HPV-39 (N=2141;2114)	21	23		
HPV-45 (N=2150;2125)	5	23		
HPV-51 (N=2115;2107)	38	34		
HPV-52 (N=2103;2095)	25	22		
HPV-56 (N=2144;2115)	15	28		
HPV-58 (N=2142;2128)	19	13		
HPV-59 (N=2147;2120)	9	22		
HPV-66 (N=2133;2117)	22	43		
HPV-68 (N=2128;2120)	15	15		
HPV-31/45 (N=2165;2146)	10	44		
HPV-31/45/33/52/58 (N=2169;2148)	56	78		
HPV-39/45/59/68 (N=2169;2148)	49	74		
HPV-31/33/35/52/58 (N=2169;2148)	56	70		
HPV-31/45/33/52/58/35/39/51/56/59 (N=2169;2148)	119	160		
HPV-HRW (N=2169;2148)	143	192		
HPV-HR (N=2169;2148)	145	223		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with histopathologically confirmed reduction of local cervical therapy.

End point title	Number of subjects with histopathologically confirmed reduction of local cervical therapy.
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End point description:

Detection was done on all subjects irrespective of their baseline HPV DNA status.

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2733	2735		
Units: Subjects				
Subjects	88	110		

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of subjects with first colposcopy.**

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End point title	Number of subjects with first colposcopy.
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End point description:

DNA status.

End point type	Secondary
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End point timeframe:

Up to Month 84

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End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2734	2736		
Units: Subjects				
Subjects	506	560		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection .**

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End point title	Number of subjects with persistent infection (6-month definition) with human papillomavirus (HPV)-16 or HPV-18 and/or with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 and/or -18 cervical infection .
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. CIN1+ was defined as CIN grades 1, 2 and 3, adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus.

End point type	Secondary
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End point timeframe:

Up to Month 84

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End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2768	2778		
Units: Subjects				
HPV-16/18	93	209		
HPV-16	66	152		
HPV-18	32	71		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-confirmed CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18 and/or with histopathologically-confirmed CIN1+ associated with HPV-16 and/or -18 cervical infection detected using the HPV Type Assignment Algorithm (TAA).
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End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type(s) by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done on all subjects irrespective of their baseline HPV DNA and serostatus. The lesion was assigned to an HPV type found in the lesion if (1) the same HPV type was found in at least 1 of the 2 (closest) preceding cytology samples, or (2) none of the HPV types found in the lesion were found in any of the 2 preceding cytology samples (isolate HPV types).

End point type	Secondary
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End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2768	2778		
Units: Subjects				
HPV-16/18	92	206		
HPV-16	65	151		
HPV-18	30	68		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of seroconverted subjects against HPV-16 in the immunogenicity subset.**

End point title	Number of seroconverted subjects against HPV-16 in the immunogenicity subset.
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End point description:

Seroconversion was defined as the appearance of antibodies (i.e.; titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination. HPV-16 assay cut-off value was defined as greater than or equal to 8 ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 8 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 8 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites N≥1000, at least 250 per region.

End point type	Secondary
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End point timeframe:

At pre-vaccination and at Month 60, 72 and 84.

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	260		
Units: Subjects				
Sero- at Month 60 (N=275;251)	275	11		
Sero- at Month 72 (N=277;260)	276	5		
Sero- at Month 84 (N=275;255)	273	2		
Sero+ at Month 60 (N=99,95)	99	79		
Sero+ at Month 72 (N=99,102)	99	57		
Sero+ at Month 84 (N=95,101)	95	51		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of seroconverted subjects against HPV-18 in the immunogenicity subset.**

End point title	Number of seroconverted subjects against HPV-18 in the immunogenicity subset.
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End point description:

Seroconversion was defined as the appearance of antibodies (i.e.; titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination. HPV-18 assay cut-off value was defined as greater than or equal to 7 ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 7 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 7 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites N≥1000, at least 250 per region.

End point type	Secondary
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End point timeframe:

At pre-vaccination and at Month 60, 72 and 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	254		
Units: Subjects				
Sero- at Month 60 (N=268;246)	266	11		
Sero- at Month 72 (N=269;254)	261	3		
Sero- at month 84 (N=268;248)	257	3		
Sero+ at Month 60 (N=101;91)	101	58		
Sero+ at Month 72 (N=103;99)	103	32		
Sero+ at Month 84 (N=98;98)	98	32		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Geometric mean concentrations (GMCs) against HPV-16 antibody in the immunogenicity subset.

End point title	Geometric mean concentrations (GMCs) against HPV-16 antibody in the immunogenicity subset.
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End point description:

GMCs were expressed in ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 8 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 8 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites (N≥1000, at least 250 per region).

End point type	Secondary
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End point timeframe:

At pre-vaccination and at Month 60, 72 and 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	260		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Sero- at Month 60 (N=275;251)	447.1 (394.3 to 507)	4.3 (4.1 to 4.5)		
Sero- at Month 72 (N=277;260)	412.8 (364 to 468.1)	9.8 (9.5 to 10)		
Sero- at Month 84 (N=275;255)	381 (334.7 to 433.8)	9.6 (9.4 to 9.9)		
Sero+ at Month 60 (N=99;95)	943 (749.2 to 1187)	24.7 (24.7 to 31.7)		
Sero+ at Month 72 (N=99;102)	1053.7 (841 to 1320.3)	25.6 (20.7 to 31.5)		
Sero+ at Month 84 (N=95;101)	954.3 (755.3 to 1205.8)	23.9 (19.3 to 29.5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Geometric mean concentrations (GMCs) against HPV-18 antibody in the immunogenicity subset.

End point title	Geometric mean concentrations (GMCs) against HPV-18 antibody in the immunogenicity subset.
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End point description:

GMCs were expressed in ELISA units per milliliter (EL.U/mL). Seronegative (Sero-) subjects are subjects who had an antibody concentration below 7 EL.U/mL prior to vaccination. Seropositive (Sero+) subjects are subjects who had an antibody concentration equal to or above 7 EL.U/mL prior to vaccination. Immuno subset=subjects from selected sites (N≥1000, at least 250 per region).

End point type	Secondary
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End point timeframe:

At pre-vaccination and at Month 60, 72 and 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	254		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Sero- at Month 60 (N=268;246)	174.3 (151.2 to 200.8)	3.8 (3.6 to 4)		
Sero- at Month 72 (N=269;254)	177.7 (154.1 to 204.8)	9.2 (9 to 9.5)		
Sero- at Month 84 (N=268;248)	166.2 (143.4 to 192.7)	9.1 (9 to 9.3)		
Sero+ at Month 60 (N=101;91)	306 (245.7 to 380.9)	12.9 (9.8 to 16.9)		
Sero+ at Month 72 (N=103;99)	324.8 (264.3 to 399.1)	16.2 (13.3 to 19.6)		
Sero+ at Month 84 (N=98;98)	302.2 (243.4 to 375.2)	16.5 (13.4 to 20.4)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting related or fatal serious adverse event.

End point title	Number of subjects reporting related or fatal serious adverse
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event.

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.

End point type Secondary

End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2877	2870		
Units: Subjects				
Fatal AEs	13	5		
Related SAEs	5	8		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects reporting any AE/SAE leading to premature discontinuation of the study.

End point title Number of subjects reporting any AE/SAE leading to premature discontinuation of the study.

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. 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.

End point type Secondary

End point timeframe:

Up to Month 84

End point values	Cervarix Group	Aluminium Hydroxide Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2877	2870		
Units: Subjects				
AEs/SAEs	28	14		



## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

SAEs: from the beginning of the study up to Month 84. Unsolicited AEs: within 30 days (Days 0-29) post-vaccination period). Solicited AEs: During the 7-day (Days 0-6) post-vaccination period.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Aluminium Hydroxide Group
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Reporting group description:

Subjects received 3 doses of Aluminium Hydroxide [Al(OH)<sub>3</sub>]. Aluminium Hydroxide was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.

Reporting group title	Cervarix Group
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Reporting group description:

Subjects received 3 doses of Cervarix™ vaccine. Cervarix vaccine was administered intramuscularly into the deltoid region of the non-dominant arm according to a 0, 1, 6 months schedule.

Serious adverse events	Aluminium Hydroxide Group	Cervarix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	269 / 2871 (9.37%)	291 / 2881 (10.10%)	
number of deaths (all causes)	5	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	9 / 2871 (0.31%)	13 / 2881 (0.45%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	3 / 2871 (0.10%)	4 / 2881 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian adenoma			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			

subjects affected / exposed	3 / 2871 (0.10%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic astrocytoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer female			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix cancer metastatic			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hodgkin's disease			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposarcoma			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mediastinum neoplasm			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngeal cancer			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal oncocytoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Teratoma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal adenocarcinoma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 2871 (0.07%)	4 / 2881 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous complete			
subjects affected / exposed	16 / 2871 (0.56%)	19 / 2881 (0.66%)	
occurrences causally related to treatment / all	2 / 16	2 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous incomplete			
subjects affected / exposed	13 / 2871 (0.45%)	18 / 2881 (0.62%)	
occurrences causally related to treatment / all	0 / 13	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abortion missed			
subjects affected / exposed	11 / 2871 (0.38%)	10 / 2881 (0.35%)	
occurrences causally related to treatment / all	1 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blighted ovum			
subjects affected / exposed	7 / 2871 (0.24%)	6 / 2881 (0.21%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	7 / 2871 (0.24%)	4 / 2881 (0.14%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	3 / 2871 (0.10%)	7 / 2881 (0.24%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	5 / 2871 (0.17%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			
subjects affected / exposed	2 / 2871 (0.07%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured ectopic pregnancy			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrested labour			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational hypertension			



subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	12 / 2871 (0.42%)	13 / 2881 (0.45%)	
occurrences causally related to treatment / all	2 / 12	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature delivery			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion complete			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage in pregnancy			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarum			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta accreta			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained products of conception			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stillbirth			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged labour			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ill-defined disorder			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 2871 (0.00%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anaphylactic reaction			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	6 / 2871 (0.21%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	3 / 2871 (0.10%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	3 / 2871 (0.10%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bartholin's cyst			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenomyosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexal torsion			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholinitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colpocoele			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmenorrhoea			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endosalpingiosis			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital prolapse			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menometrorrhagia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic prolapse			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycystic ovaries			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine atony			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cyst			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 2871 (0.07%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal cyst			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal disorder			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus disorder			



subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 2871 (0.03%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 2871 (0.00%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Bipolar disorder			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia nervosa			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	3 / 2871 (0.10%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaesthetic complication pulmonary			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod sting			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar nerve injury			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention postoperative			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			

subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Bronchogenic cyst			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac arrest			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 2871 (0.00%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	4 / 2871 (0.14%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			



subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral cyst			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic coma			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery dissection			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placental transfusion syndrome			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ear and labyrinth disorders</b>			
Vertigo			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			

Angle closure glaucoma			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 2871 (0.07%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 2871 (0.07%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eiploic appendagitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	9 / 2871 (0.31%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 2871 (0.07%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	3 / 2871 (0.10%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			



Nephrolithiasis			
subjects affected / exposed	3 / 2871 (0.10%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	2 / 2871 (0.07%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ureteric obstruction			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Addison's disease			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cyst			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 2871 (0.07%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	3 / 2871 (0.10%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lupus-like syndrome			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periostitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Synovial cyst			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	12 / 2871 (0.42%)	13 / 2881 (0.45%)	
occurrences causally related to treatment / all	0 / 12	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 2871 (0.03%)	9 / 2881 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 2871 (0.10%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 2871 (0.10%)	5 / 2881 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 2871 (0.03%)	6 / 2881 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 2871 (0.03%)	3 / 2881 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 2871 (0.03%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Salpingitis			
subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amniotic cavity infection			

subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burn infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chlamydial infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis klebsiella			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lyme disease			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opisthorchiasis			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pasteurella infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			



subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tonsillitis			

subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 2871 (0.03%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 2871 (0.03%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	3 / 2871 (0.10%)	0 / 2881 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 2871 (0.00%)	2 / 2881 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesterosis			
subjects affected / exposed	0 / 2871 (0.00%)	1 / 2881 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Aluminium Hydroxide Group	Cervarix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1862 / 2871 (64.86%)	2411 / 2881 (83.69%)	
Nervous system disorders			
Headache (unsolicited)			
subjects affected / exposed	222 / 2871 (7.73%)	203 / 2881 (7.05%)	
occurrences (all)	222	203	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	1862 / 2871 (64.86%)	2411 / 2881 (83.69%)	
occurrences (all)	1862	2411	
Redness			
alternative assessment type: Systematic			

subjects affected / exposed	530 / 2871 (18.46%)	1058 / 2881 (36.72%)	
occurrences (all)	530	1058	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	428 / 2871 (14.91%)	1080 / 2881 (37.49%)	
occurrences (all)	428	1080	
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	439 / 2871 (15.29%)	580 / 2881 (20.13%)	
occurrences (all)	439	580	
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	916 / 2871 (31.91%)	1116 / 2881 (38.74%)	
occurrences (all)	916	1116	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	248 / 2871 (8.64%)	308 / 2881 (10.69%)	
occurrences (all)	248	308	
Gastrointestinal			
alternative assessment type: Systematic			
subjects affected / exposed	592 / 2871 (20.62%)	664 / 2881 (23.05%)	
occurrences (all)	592	664	
Headache (solicited general symptom)			
alternative assessment type: Systematic			
subjects affected / exposed	1074 / 2871 (37.41%)	1165 / 2881 (40.44%)	
occurrences (all)	1074	1165	
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	622 / 2871 (21.66%)	878 / 2881 (30.48%)	
occurrences (all)	622	878	
Rash			
alternative assessment type: Systematic			

subjects affected / exposed	124 / 2871 (4.32%)	185 / 2881 (6.42%)	
occurrences (all)	124	185	
Urticaria			
alternative assessment type: Systematic			
subjects affected / exposed	201 / 2871 (7.00%)	258 / 2881 (8.96%)	
occurrences (all)	201	258	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2006	Study endpoints were amended following a request from the FDA and study procedures were amended following the licensure of an HPV vaccine by a competitor. In addition a safety interim analysis is now planned.
30 July 2008	The protocol has been amended to add an additional gynaecological examination, to enlarge the length of study visit intervals and to clarify the procedures for cross-over immunization and follow-up gynaecological care after study completion (as requested by the IDMC). In addition, a new Investigator's Brochure, Edition 8 dated August 2008, has been issued since the previous submission, which replaces the Investigator's Brochure, Edition 7 dated August 2007.
23 October 2008	As requested by the FDA, the principle analysis of efficacy endpoints will be performed on the according-to-protocol (ATP) cohort for efficacy, excluding the 15% subset of women enrolled with a prior history of HPV disease/infection. In order to maintain the power for the primary endpoint, two additional study visits (at Months 42 and 48) were added to extend the total study duration by 12 months.
24 March 2010	Because the HPV-015 study population is sexually active, it is important to also evaluate the vaccine efficacy in all women, including those who have been exposed to HPV (i.e., in the Total Vaccinated cohort [TVC]). In order to demonstrate this impact, the study protocol has been amended to extend by a maximum of three additional years, resulting in a maximum total length of seven years (84 months) follow-up.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported