



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">• New data added to full data set• Correction of full data set 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 |
|-----------------------|--------|

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? |
|--------------------------------|

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 | Efficacy, Ethical reason, Safety, 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:

| Subjects enrolled per age group | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 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 |
|----------------------------|-----------------------------|

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 |
|------------------------------|-----|

| | |
|------------------|----------------|
| Arm title | Cervarix Group |
|------------------|----------------|

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.

| | |
|------------------|---------------------------|
| Arm title | Aluminium Hydroxide Group |
|------------------|---------------------------|

Arm 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.

| | |
|----------|--------------------|
| Arm type | Placebo Comparator |
|----------|--------------------|

| | |
|--|-------------------|
| 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.

| Number of subjects in period 1^[1] | 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)₃]. 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. ^[1] |
|-----------------|--|

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 |
|----------------|---------|

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). ^[2] |
|-----------------|---|

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 |
|----------------|---------|

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. ^[3] |
|-----------------|---|

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 |
|----------------|---------|

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). ^[4] |
|-----------------|---|

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 |
|----------------|---------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
| 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 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. |
|-----------------|---|

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. |
|-----------------|--|

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 |
|-----------------|--|

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 |
|-----------------|--|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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) | 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 | |

| End point values | 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 |
|-----------------|--|

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 | 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 |
|-----------------|--|

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 |
|----------------|-----------|

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). |
|-----------------|--|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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. |
|-----------------|---|

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. |
|-----------------|---|

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 |
|----------------|-----------|

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: 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. |
|-----------------|--|

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 |
|----------------|-----------|

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. |
|-----------------|--|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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 |
|----------------|-----------|

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). |
|-----------------|---|

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 |
|----------------|-----------|

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). |
|-----------------|---|

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 |
|----------------|-----------|

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). |
|-----------------|--|

End point description:

NOCDs include autoimmune disorders, asthma and type I diabetes.

| | |
|----------------|-----------|
| 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 | 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). |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| 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 | 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). |
|-----------------|---|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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. |
|-----------------|---|

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 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. |
|-----------------|---|

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 |
|----------------|-----------|

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. |
|-----------------|--|

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 |
|----------------|-----------|

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. |
|-----------------|--|

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. |
|-----------------|--|

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 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

Secondary: Number of subjects with first colposcopy.

| | |
|-----------------|---|
| End point title | Number of subjects with first colposcopy. |
|-----------------|---|

End point description:

DNA status.

| | |
|----------------|-----------|
| 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 | 2734 | 2736 | | |
| Units: Subjects | | | | |
| Subjects | 506 | 560 | | |

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 . |
|-----------------|--|

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 |
|----------------|-----------|

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 | 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). |
|-----------------|--|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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 |
|----------------|-----------|

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. |
|-----------------|---|

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 |
|----------------|-----------|

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. |
|-----------------|--|

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 |
|----------------|-----------|

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. |
| 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 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 |
|-----------------|---|

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

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| 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.

| | |
|-----------------------|----------------|
| 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.

| 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 | |
| Blood and lymphatic system disorders | | | |
| 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 | |
| Ear and labyrinth disorders | | | |
| 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 | |
| Eye disorders | | | |

| | | | |
|---|------------------|------------------|--|
| 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 | |
| Gastrooesophageal 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 | | | |

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|---|------------------|------------------|--|
| 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 | |

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| 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 %

| Non-serious adverse events | 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