# Clinical trial results:
# A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™, Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 16- to 26-Year-Old Women

## Summary

| | |
|---|---|
| EudraCT number | 2007-003528-39 |
| Trial protocol | DK SE DE AT Outside EU/EEA |
| Global end of trial date | 07 July 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 January 2017 |
| First version publication date | 04 January 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | V503-001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00543543 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000654-PIP01-09 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 07 July 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety, efficacy, and immunogenicity of V503 in comparison to GARDASIL. The primary hypotheses tested in the study were 1) V503 administered to 16- to 26-year-old adolescents and young women is generally well-tolerated, 2) V503 reduces combined incidence of Human Papillomavirus (HPV) Type 31/33/45/52/58-related disease compared with GARDASIL, and 3) V503 induces non-inferior geometric mean titers for HPV Type 6/11/16/18 antibodies compared with GARDASIL.
The study included a dose-finding evaluation of a 3-dose regimen of V503 and GARDASIL, a safety/efficacy evaluation of a 3-dose regimen of the selected V503 dose formulation and GARDASIL, and an extension consisting of 2 substudies: an evaluation of immune memory in participants receiving a fourth vaccination with V503 (Cohort 1), and an opportunity for participants who received GARDASIL in the Base Study to receive a 3-dose regimen of V503 (Cohort 2).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure(s) defined for this individual study was (were) in place for the protection of trial subjects: participants who received GARDASIL in the Base Study will have the opportunity to receive a 3-dose regimen of V503 in the study extension (Cohort 2).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 24 September 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 168 |
| Country: Number of subjects enrolled | Brazil: 765 |
| Country: Number of subjects enrolled | Canada: 1442 |
| Country: Number of subjects enrolled | Chile: 140 |
| Country: Number of subjects enrolled | Colombia: 2499 |
| Country: Number of subjects enrolled | Denmark: 3731 |
| Country: Number of subjects enrolled | Germany: 194 |
| Country: Number of subjects enrolled | Hong Kong: 160 |
| Country: Number of subjects enrolled | Japan: 254 |
| Country: Number of subjects enrolled | Korea, Republic of: 307 |
| Country: Number of subjects enrolled | New Zealand: 97 |

| | |
|---|---|
| Country: Number of subjects enrolled | Norway: 710 |
| Country: Number of subjects enrolled | Peru: 785 |
| Country: Number of subjects enrolled | Puerto Rico: 42 |
| Country: Number of subjects enrolled | Sweden: 128 |
| Country: Number of subjects enrolled | Taiwan: 600 |
| Country: Number of subjects enrolled | Thailand: 465 |
| Country: Number of subjects enrolled | United States: 1572 |
| Country: Number of subjects enrolled | Mexico: 781 |
| Worldwide total number of subjects | 14840 |
| EEA total number of subjects | 4931 |

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) | 343 |
| Adults (18-64 years) | 14497 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study enrolled healthy young women 16 to 26 years of age.

### Pre-assignment

Screening details:

A total of 15,334 participants were screened and 14,840 were randomized into the study.

### Period 1

| | |
|---|---|
| Period 1 title | Base Study |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Low-dose V503 |

Arm description:

V503 (9-Valent Human Papillomavirus [HPV] Vaccine) low-dose 0.5 mL injection in a 3-dose regimen in the Base Study.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| | |
|---|---|
| **Arm title** | Mid-dose V503 |

Arm description:

V503 mid-dose 0.5 mL injection in a 3-dose regimen in the Base Study. A subset of participants will receive a fourth V503 mid-dose vaccination in the extension study (Cohort 1).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| | |
|---|---|
| **Arm title** | High-dose V503 |

Arm description:

V503 high-dose 0.5 mL injection in a 3-dose regimen in the Base Study

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| | |
|---|---|
| **Arm title** | Gardasil |

Arm description:

Gardasil (4-Valent HPV Vaccine) 0.5 mL injection in a 3-dose regimen in the Base Study. Participants will be offered the V503 mid-dose 3-dose regimen in the extension study (Cohort 2).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GARDASIL (4-Valent HPV [Types 6, 11, 16, and 18] L1 virus-like particle vaccine) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| **Number of subjects in period 1** | Low-dose V503 | Mid-dose V503 | High-dose V503 |
|---|---|---|---|
| Started | 315 | 7106 | 310 |
| Completed 3 vaccinations in Base Study | 300 | 6928 | 297 |
| Completed | 295 | 5854 | 296 |
| Not completed | 20 | 1252 | 14 |
| Consent withdrawn by subject | 7 | 482 | 5 |
| Physician decision | - | 4 | - |
| Adverse event, non-fatal | 1 | 11 | - |
| Lost to follow-up | 12 | 749 | 9 |
| Protocol deviation | - | 6 | - |

| **Number of subjects in period 1** | Gardasil |
|---|---|
| Started | 7109 |
| Completed 3 vaccinations in Base Study | 6934 |
| Completed | 5887 |
| Not completed | 1222 |
| Consent withdrawn by subject | 503 |
| Physician decision | 7 |
| Adverse event, non-fatal | 5 |
| Lost to follow-up | 701 |
| Protocol deviation | 6 |

## Period 2

| | |
|---|---|
| Period 2 title | Extension Study |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Mid-dose V503 (Cohort 1) |

Arm description:

V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL fourth dose administration on Base Study participants who were randomized to receive a 3-dose regimen of V503 (9-Valent HPV) mid-dose 0.5 mL (Cohort 1).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| | |
|---|---|
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle at Month 60 in the Extension Study

| | |
|---|---|
| **Arm title** | Mid-dose V503 (Cohort 2) |

Arm description:

V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL 3-dose regimen administration on Base Study participants who were randomized to receive a 3-dose regimen of Gardasil (4-Valent HPV Vaccine) (Cohort 2).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | V503 9-valent HPV (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle at Month 60, 62 and 66 of the Extension Study

| | |
|---|---|
| Investigational medicinal product name | GARDASIL (4-Valent HPV [Types 6, 11, 16, and 18] L1 virus-like particle vaccine) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL injection in the non-dominant deltoid muscle on Day 1, Month 2 and Month 6 of the Base Study

| **Number of subjects in period 2[1]** | Mid-dose V503 (Cohort 1) | Mid-dose V503 (Cohort 2) |
|---|---|---|
| Started | 150 | 3050 |
| Completed | 150 | 2824 |
| Not completed | 0 | 226 |
| Physician decision | - | 7 |
| Consent withdrawn by subject | - | 120 |
| Adverse event, non-fatal | - | 5 |
| Pregnancy | - | 6 |
| Lost to follow-up | - | 77 |
| Protocol deviation | - | 11 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Enrollment in Cohorts 1 and 2 was voluntary; not all eligible participants enrolled in these cohorts.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Low-dose V503 |
| Reporting group description: | |
| V503 (9-Valent Human Papillomavirus [HPV] Vaccine) low-dose 0.5 mL injection in a 3-dose regimen in the Base Study. | |
| Reporting group title | Mid-dose V503 |
| Reporting group description: | |
| V503 mid-dose 0.5 mL injection in a 3-dose regimen in the Base Study. A subset of participants will receive a fourth V503 mid-dose vaccination in the extension study (Cohort 1). | |
| Reporting group title | High-dose V503 |
| Reporting group description: | |
| V503 high-dose 0.5 mL injection in a 3-dose regimen in the Base Study | |
| Reporting group title | Gardasil |
| Reporting group description: | |
| Gardasil (4-Valent HPV Vaccine) 0.5 mL injection in a 3-dose regimen in the Base Study. Participants will be offered the V503 mid-dose 3-dose regimen in the extension study (Cohort 2). | |

| Reporting group values | Low-dose V503 | Mid-dose V503 | High-dose V503 |
|---|---|---|---|
| Number of subjects | 315 | 7106 | 310 |
| Age Categorical<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 3 | 170 | 3 |
| Adults (18-64 years) | 312 | 6936 | 307 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 21.7 | 21.9 | 21.9 |
| standard deviation | ± 2.4 | ± 2.5 | ± 2.4 |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 315 | 7106 | 310 |
| Male | 0 | 0 | 0 |

| Reporting group values | Gardasil | Total | |
|---|---|---|---|
| Number of subjects | 7109 | 14840 | |
| Age Categorical<br>Units: Subjects | | | |
| Adolescents (12-17 years) | 167 | 343 | |
| Adults (18-64 years) | 6942 | 14497 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 21.8 | | |
| standard deviation | ± 2.5 | - | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 7109 | 14840 | |
| Male | 0 | 0 | |

## End points

### End points reporting groups

| Reporting group title | Low-dose V503 |
|---|---|
| Reporting group description: | |
| V503 (9-Valent Human Papillomavirus [HPV] Vaccine) low-dose 0.5 mL injection in a 3-dose regimen in the Base Study. | |
| Reporting group title | Mid-dose V503 |
| Reporting group description: | |
| V503 mid-dose 0.5 mL injection in a 3-dose regimen in the Base Study. A subset of participants will receive a fourth V503 mid-dose vaccination in the extension study (Cohort 1). | |
| Reporting group title | High-dose V503 |
| Reporting group description: | |
| V503 high-dose 0.5 mL injection in a 3-dose regimen in the Base Study | |
| Reporting group title | Gardasil |
| Reporting group description: | |
| Gardasil (4-Valent HPV Vaccine) 0.5 mL injection in a 3-dose regimen in the Base Study. Participants will be offered the V503 mid-dose 3-dose regimen in the extension study (Cohort 2). | |
| Reporting group title | Mid-dose V503 (Cohort 1) |
| Reporting group description: | |
| V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL fourth dose administration on Base Study participants who were randomized to receive a 3-dose regimen of V503 (9-Valent HPV) mid-dose 0.5 mL (Cohort 1). | |
| Reporting group title | Mid-dose V503 (Cohort 2) |
| Reporting group description: | |
| V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL 3-dose regimen administration on Base Study participants who were randomized to receive a 3-dose regimen of Gardasil (4-Valent HPV Vaccine) (Cohort 2). | |

### Primary: Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related High-Grade Disease (Test of Hypothesis)

| End point title | Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related High-Grade Disease (Test of Hypothesis)[1] |
|---|---|
| End point description: | |
| HPV Type 31/33/45/52/58-related high-grade Cervical Intraepithelial Neoplasia (CIN 2/3), Adenocarcinoma in Situ (AIS), Invasive Cervical Carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer were determined by clinical/pathologic criteria and positive Polymerase Chain Reaction (PCR) assay for virus subtype. This outcome measure reports data based on the protocol-specified plan of conducting hypothesis testing when at least 30 cases had accumulated. Disease incidence was defined as the number of primary efficacy cases per 10,000 person-years of follow-up in a treatment arm. The Per-protocol Efficacy population included all participants who received all 3 vaccinations of mid-dose V503 or Gardasil within acceptable day ranges, were seronegative at Day 1 and PCR negative at Day 1 through Day 7 to the relevant HPV types, and had at least 1 follow-up visit following Month 7. | |
| End point type | Primary |
| End point timeframe: | |
| From Month 7 until >=30 cases accumulate, up to Month 54 in the base study | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applied only to the Mid-dose V503 and Gardasil groups.

| End point values | Mid-dose V503 | Gardasil | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6016 | 6017 | | |
| Units: Cases per 10,000 person-years follow-up | | | | |
| number (not applicable) | 0.5 | 15.8 | | |

### Statistical analyses

| Statistical analysis title | V503 Vaccine Efficacy |
|---|---|
| Statistical analysis description: | |
| Vaccine efficacy = 100 * [1 - (incidence rate with V503 / incidence rate with Gardasil)] | |
| Comparison groups | Mid-dose V503 v Gardasil |
| Number of subjects included in analysis | 12033 |
| Analysis specification | Pre-specified |
| Analysis type | other[2] |
| P-value | < 0.0001 |
| Method | Chan and Bohidar Exact Binomial |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 96.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 80.9 |
| upper limit | 99.8 |

Notes:

[2] - The pre-specified success criterion was a lower bound of the 95% confidence interval of observed efficacy of >25%

### Primary: Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related High-Grade Disease (End-of-study Update)

| End point title | Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related High-Grade Disease (End-of-study Update)[3] |
|---|---|

End point description:

HPV Type 31/33/45/52/58-related high-grade Cervical Intraepithelial Neoplasia (CIN 2/3), Adenocarcinoma in Situ (AIS), Invasive Cervical Carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer were determined by clinical/pathologic criteria and positive Polymerase Chain Reaction (PCR) assay for virus subtype. This outcome measure reports cumulative study data through 10 March 2014. Disease incidence was defined as the number of primary efficacy cases per 10,000 person-years of follow-up in a treatment arm. The Per-protocol Efficacy population included all participants who received all 3 vaccinations of mid-dose V503 or Gardasil within acceptable day ranges, were seronegative at Day 1 and PCR negative at Day 1 through Day 7 to the relevant HPV types, and had at least 1 follow-up visit following Month 7.

| End point type | Primary |
|---|---|

End point timeframe:

From Month 7 up to Month 54 in the Base Study

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applied only to the mid-dose V503 and Gardasil groups.

| End point values | Mid-dose V503 | Gardasil | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6016 | 6017 | | |
| Units: Cases per 10,000 person-years follow-up | | | | |
| number (not applicable) | 0.5 | 19 | | |

**Statistical analyses**

| Statistical analysis title | V503 Vaccine Efficacy (End-of-Study Update) |
|---|---|
| Statistical analysis description: | |
| Vaccine efficacy = 100 * [1 - (incidence rate with V503 / incidence rate with Gardasil)] | |
| Comparison groups | Mid-dose V503 v Gardasil |
| Number of subjects included in analysis | 12033 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 97.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 85 |
| upper limit | 99.9 |

Notes:

[4] - The pre-specified success criterion was a lower bound of the 95% confidence interval of observed efficacy of >25%

**Primary: Base Study: Geometric Mean Titers (GMTs) to HPV Types 6/11/16/18/31/33/45/52/58**

| End point title | Base Study: Geometric Mean Titers (GMTs) to HPV Types 6/11/16/18/31/33/45/52/58[5] |
|---|---|

End point description:

Serum antibodies to HPV types 6/11/16/18/31/33/45/52/58 were measured with a Competitive Luminex Immunoassay. Titers are reported in milli Merck Units/mL. Statistical analysis was performed only for HPV types contained in both vaccines. The Per-protocol Immunogenicity population included all participants who were not protocol violators, received all 3vaccinations of mid-dose V503 or Gardasil within acceptable ranges, were seronegative at Day 1 and PCR negative from Day 1 to Month 7 for the relevant HPV types, and had a Month 7 serum sample collected within an acceptable range. A value of 9999 means less than the limit of quantification. Statistical analysis was performed only for HPV types contained in both vaccines.

| End point type | Primary |
|---|---|

End point timeframe:

4 weeks postdose 3 in the Base Study

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applied only to the mid-dose V503 and Gardasil groups.

| End point values | Mid-dose V503 | Gardasil | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6792 | 6795 | | |
| Units: milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV Type 6 (n=3993, 3975) | 893.1 (871.7 to 915.1) | 875.2 (854.2 to 896.8) | | |
| Anti-HPV Type 11 (n=3995, 3982) | 666.3 (649.6 to 683.4) | 830 (809.2 to 851.4) | | |
| Anti-HPV Type 16 (n=4032, 4062) | 3131.1 (3057.1 to 3206.9) | 3156.6 (3082.3 to 3232.7) | | |
| Anti-HPV Type 18 (n=4539, 4541) | 804.6 (782.7 to 827.1) | 678.7 (660.2 to 697.7) | | |
| Anti-HPV Type 31 (n=4466, 4377) | 658.4 (636.7 to 680.9) | 9.7 (9.4 to 10.1) | | |
| Anti-HPV Type 33 (n=4702, 4691) | 415.9 (405.6 to 426.4) | 9999 (9999 to 9999) | | |
| Anti-HPV Type 45 (n=4792, 4750) | 252.8 (246.2 to 259.6) | 9999 (9999 to 9999) | | |
| Anti-HPV Type 52 (n=4455, 4335) | 379.7 (371.6 to 388) | 9999 (9999 to 9999) | | |
| Anti-HPV Type 58 (n=4486, 4446) | 482.5 (469.9 to 495.3) | 9999 (9999 to 9999) | | |

**Statistical analyses**

| Statistical analysis title | Non-inferiority anti-HPV Type 6 |
|---|---|
| Statistical analysis description: | |
| Non-inferiority required that the lower bound of the two-sided confidence interval (CI) of the GMT ratio was >0.67 | |
| Comparison groups | Mid-dose V503 v Gardasil |
| Number of subjects included in analysis | 13587 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | GMT ratio = GMT (V503) / GMT (Gardasil) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.06 |

| Statistical analysis title | Non-inferiority anti-HPV Type 11 |
|---|---|
| Statistical analysis description: | |
| Non-inferiority required that the lower bound of the two-sided confidence interval (CI) of the GMT ratio was >0.67 | |
| Comparison groups | Mid-dose V503 v Gardasil |

| | |
|---|---|
| Number of subjects included in analysis | 13587 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | GMT ratio = GMT (V503) / GMT (Gardasil) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 0.83 |

| **Statistical analysis title** | Non-inferiority anti-HPV Type 16 |
|---|---|
| Statistical analysis description: | |
| Non-inferiority required that the lower bound of the two-sided CI of the GMT ratio was >0.67 | |
| Comparison groups | Mid-dose V503 v Gardasil |
| Number of subjects included in analysis | 13587 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | GMT ratio = GMT (V503) / GMT (Gardasil) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.03 |

| **Statistical analysis title** | Non-inferiority anti-HPV Type 18 |
|---|---|
| Statistical analysis description: | |
| Non-inferiority required that the lower bound of the two-sided CI of the GMT ratio was >0.67 | |
| Comparison groups | Mid-dose V503 v Gardasil |
| Number of subjects included in analysis | 13587 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | ANOVA |
| Parameter estimate | GMT ratio = GMT (V503) / GMT (Gardasil) |
| Point estimate | 1.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 1.23 |

## Primary: Base Study: Percentage of Participants With One or More Adverse Event

| End point title | Base Study: Percentage of Participants With One or More Adverse Event[6] |
|---|---|

End point description:

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. The analysis population included all participants who received >=1 vaccination and had safety follow-up.

| End point type | Primary |
|---|---|

End point timeframe:

Up to Month 7 (low- and high-dose V503) or up to Month 54 (mid-dose V503 and Gardasil)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Percentage of Participants With One or More Adverse Event.

| End point values | Low-dose V503 | Mid-dose V503 | High-dose V503 | Gardasil |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 310 | 7071 | 305 | 7078 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 92.6 | 94.2 | 92.8 | 91.1 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Base Study: Percentage of Participants With One or More Injection-site Adverse Event

| End point title | Base Study: Percentage of Participants With One or More Injection-site Adverse Event[7] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. AEs such as redness, swelling, and pain/tenderness/soreness at the injection site were recorded. The analysis population included all participants who received >=1 vaccination and had safety follow-up.

| End point type | Primary |
|---|---|

End point timeframe:

Up to Day 5 after any vaccination in the Base Study

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Percentage of Participants With One or More Injection-site Adverse Event.

| End point values | Low-dose V503 | Mid-dose V503 | High-dose V503 | Gardasil |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 310 | 7071 | 305 | 7078 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 87.7 | 90.7 | 90.5 | 84.9 |

### Statistical analyses

No statistical analyses for this end point

### Primary: Base Study: Percentage of Participants With One or More Non-injection-site (Systemic) Adverse Event

| End point title | Base Study: Percentage of Participants With One or More Non-injection-site (Systemic) Adverse Event[8] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. Systemic AEs were those not categorized as injection-site AEs. The analysis population included all participants who received >=1 vaccination and had safety follow-up.

| End point type | Primary |
|---|---|

End point timeframe:

Up to Day 15 after any vaccination in the Base Study

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Percentage of Participants With One or More Non-injection-site (Systemic) Adverse Event.

| End point values | Low-dose V503 | Mid-dose V503 | High-dose V503 | Gardasil |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 310 | 7071 | 305 | 7078 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 53.5 | 55.8 | 51.1 | 54.9 |

### Statistical analyses

No statistical analyses for this end point

### Primary: Base Study: Percentage of Participants With One or More Vaccine-related Adverse Event

| End point title | Base Study: Percentage of Participants With One or More Vaccine-related Adverse Event[9] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an adverse event. An AE that is judged by the investigator to be "definitely related," "probably related," or "possibly related" to the study drug is defined as a vaccine-related AE. The analysis population included all participants who received >=1 vaccination and had

safety follow-up.

| End point type | Primary |
|---|---|

End point timeframe:

Up to Month 7 (low- and high-dose V503) or up to Month 54 (mid-dose V503 and Gardasil)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Percentage of Participants With One or More Vaccine-related Adverse Event.

| **End point values** | Low-dose V503 | Mid-dose V503 | High-dose V503 | Gardasil |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 310 | 7071 | 305 | 7078 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 90 | 92.2 | 92.8 | 87.6 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Base Study: Percentage of Participants With Study Medication Withdrawn Due to an Adverse Event

| End point title | Base Study: Percentage of Participants With Study Medication Withdrawn Due to an Adverse Event[10] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study vaccine, whether or not considered related to the use of the product. Any worsening of a preexisting condition which is temporally associated with the use of the study vaccine is also an AE. The analysis population included all participants who received >=1 vaccination and had safety follow-up.

| End point type | Primary |
|---|---|

End point timeframe:

Up to Month 6

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Percentage of Participants With Study Medication Withdrawn Due to an Adverse Event.

| **End point values** | Low-dose V503 | Mid-dose V503 | High-dose V503 | Gardasil |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 310 | 7071 | 305 | 7078 |
| Units: Percentage of participants | | | | |
| number (not applicable) | 0.6 | 0.1 | 0 | 0.1 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Extension Study (Immune Memory Substudy): Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Day 7 Postdose 4

| End point title | Extension Study (Immune Memory Substudy): Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Day 7 Postdose 4[11] |
|---|---|

End point description:

Serum antibodies to HPV types 6/11/16/18/31/33/45/52/58 were measured with a Competitive Luminex Immunoassay. Titers are reported in milli Merck Units/mL. The Per-Protocol Immunogenicity population (Cohort 1) included all participants who were not protocol violators, received all 3 vaccinations of mid-dose V503 in the Base Study and a fourth dose in the Extension Study within acceptable ranges, were seronegative at Day 1 and PCR negative from Day 1 to Month7 for the relevant HPV types, and had a Month 60 serum sample collected within an acceptable range.

| End point type | Primary |
|---|---|

End point timeframe:

Month 60 + 1 week: Day 7 postdose 4 in the Extension Study (Cohort 1)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Day 7 Postdose 4.

| **End point values** | Mid-dose V503 (Cohort 1) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 150 | | | |
| Units: milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV Type 6 (n=109) | 2180.5 (1826.2 to 2603.7) | | | |
| Anti-HPV Type 11 (n=109) | 2228.7 (1852.5 to 2681.3) | | | |
| Anti-HPV Type 16 (n=126) | 7986.3 (6795.7 to 9385.6) | | | |
| Anti-HPV Type 18 (n=138) | 2399 (2049.4 to 2808.1) | | | |
| Anti-HPV Type 31 (n=131) | 1462.2 (1263.9 to 1691.5) | | | |
| Anti-HPV Type 33 (n=137) | 1709 (1466.7 to 1991.2) | | | |
| Anti-HPV Type 45 (n=144) | 323 (277.2 to 376.5) | | | |
| Anti-HPV Type 52 (n=131) | 1078.1 (907.2 to 1281.2) | | | |
| Anti-HPV Type 58 (n=129) | 1801.8 (1530.5 to 2121.2) | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Extension Study (Immune Memory Substudy): Geometric Mean Titers to

## HPV Types 6/11/16/18/31/33/45/52/58 at Day 28 Postdose 4

| End point title | Extension Study (Immune Memory Substudy): Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Day 28 Postdose 4[12] |
|---|---|

End point description:

Serum antibodies to HPV types 6/11/16/18/31/33/45/52/58 were measured with a Competitive Luminex Immunoassay. Titers are reported in milli Merck Units/mL. The Per-Protocol Immunogenicity population (Cohort 1) included all participants who were not protocol violators, received all 3 vaccinations of mid-dose V503 in the Base Study and a fourth dose in the Extension Study within acceptable ranges, were seronegative at Day 1 and PCR negative from Day 1 to Month7 for the relevant HPV types, and had a Month 60 serum sample collected within an acceptable range.

| End point type | Primary |
|---|---|

End point timeframe:

Month 61: 28 days postdose 4 in the Extension Study (Cohort 1)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Day 28 Postdose 4.

| End point values | Mid-dose V503 (Cohort 1) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 150 | | | |
| Units: milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV Type 6 (n=109) | 2585 (2239.5 to 2983.8) | | | |
| Anti-HPV Type 11 (n=109) | 2548.7 (2191.4 to 2964.3) | | | |
| Anti-HPV Type 16 (n=123) | 10904.3 (9605.6 to 12378.7) | | | |
| Anti-HPV Type 18 (n=137) | 2907.9 (2531.1 to 3340.7) | | | |
| Anti-HPV Type 31 (n=130) | 1745.4 (1538.8 to 1979.8) | | | |
| Anti-HPV Type 33 (n=136) | 2094.9 (1848.7 to 2373.9) | | | |
| Anti-HPV Type 45 (n=143) | 440 (386.9 to 500.4) | | | |
| Anti-HPV Type 52 (n=129) | 1131.5 (991.6 to 1291.1) | | | |
| Anti-HPV Type 58 (n=127) | 2024.6 (1803.1 to 2273.2) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related

## Persistent Infection

| End point title | Base Study: Combined Incidence of HPV Type 31/33/45/52/58-related Persistent Infection[13] |
|---|---|

End point description:

Combined Incidence of HPV Type 31/33/45/52/58-related persistent infection as determined by clinical/pathologic criteria and positive Polymerase Chain Reaction (PCR) assay for virus subtype. Persistent infection was defined as infection detected in samples from >=2 consecutive visits 6 months (+/-1 month visit window) or longer apart. Incidence was defined as the number of cases of persistent infection per 10,000 person-years of follow-up in a treatment arm. The Per-protocol Efficacy population included all participants who received all 3 vaccinations of mid-dose V503 or Gardasil within acceptable day ranges, were seronegative at Day 1 and PCR negative at Day 1 through Day 7 to the relevant HPV types, and had at least 1 follow-up visit following Month 7.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to Month 54 in the Base Study

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applied only to the mid-dose V503 and Gardasil groups.

| End point values | Mid-dose V503 | Gardasil | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5941 | 5955 | | |
| Units: Cases per 10,000 person-years follow-up | | | | |
| number (not applicable) | 21.5 | 538.8 | | |

### Statistical analyses

| Statistical analysis title | Vaccine Efficacy |
|---|---|

Statistical analysis description:

Vaccine efficacy = 100 * [1 - (incidence rate with V503 / incidence rate with Gardasil)]

| Comparison groups | Mid-dose V503 v Gardasil |
|---|---|
| Number of subjects included in analysis | 11896 |
| Analysis specification | Pre-specified |
| Analysis type | other[14] |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 94.6 |
| upper limit | 97.1 |

Notes:

[14] - The pre-specified success criterion was a lower bound of the 95% confidence interval of observed efficacy of >25%

## Secondary: Base Study: Percentage of Participants Who Are Seropositive for HPV Types 6/11/16/18/31/33/45/52/58

| End point title | Base Study: Percentage of Participants Who Are Seropositive for HPV Types 6/11/16/18/31/33/45/52/58[15] |
|---|---|

End point description:

Serum antibodies to HPV types were measured with a Competitive Luminex Immunoassay. The serostatus cutoffs (milli Merck U/mL) for HPV types were as follows: HPV Type 6: ≥30; HPV Type 11: ≥16; HPV Type 16: ≥20; HPV Type 18: ≥24; HPV Type 31: ≥10; HPV Types 33, 45, 52, and 58: ≥8. The Per-protocol Immunogenicity population included all participants who were not protocol violators, received all 3 vaccinations of mid-dose V503 or Gardasil within acceptable ranges, were seronegative at Day 1 and PCR negative from Day 1 - Month 7 for the relevant HPV types, and had a Month 7 serum sample collected within an acceptable range.

| End point type | Secondary |
|---|---|

End point timeframe:

4 weeks postdose 3 in the Base Study

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint applied only to the mid-dose V503 and Gardasil groups.

| **End point values** | Mid-dose V503 | Gardasil | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6792 | 6795 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| Anti-HPV Type 6 (n=3993, 3975) | 99.8 (99.6 to 99.9) | 99.8 (99.7 to 99.9) | | |
| Anti-HPV Type 11 (n=3995, 3982) | 100 (99.9 to 100) | 99.9 (99.8 to 100) | | |
| Anti-HPV Type 16 (n=4032, 4062) | 100 (99.9 to 100) | 100 (99.9 to 100) | | |
| Anti-HPV Type 18 (n=4539, 4541) | 99.9 (99.7 to 99.9) | 99.7 (99.5 to 99.8) | | |
| Anti-HPV Type 31 (n=4466, 4377) | 99.8 (99.6 to 99.9) | 50.1 (48.7 to 51.6) | | |
| Anti-HPV Type 33 (n=4702, 4691) | 99.7 (99.5 to 99.9) | 12.7 (11.8 to 13.7) | | |
| Anti-HPV Type 45 (n=4792, 4750) | 99.6 (99.4 to 99.8) | 9.2 (8.4 to 10) | | |
| Anti-HPV Type 52 (n=4455, 4335) | 99.8 (99.6 to 99.9) | 2.6 (2.2 to 3.1) | | |
| Anti-HPV Type 58 (n=4486, 4446) | 99.8 (99.6 to 99.9) | 20.4 (19.2 to 21.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Extension Study (Immune Memory Substudy): Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Predose 4

| End point title | Extension Study (Immune Memory Substudy): Geometric Mean Titers to HPV Types 6/11/16/18/31/33/45/52/58 at Predose 4 |
|---|---|

End point description:

Serum antibodies to HPV types 6/11/16/18/31/33/45/52/58 were measured with a Competitive Luminex Immunoassay. Titers are reported in milli Merck Units/mL. The Per-Protocol Immunogenicity population (Cohort 1) included all participants who were not protocol violators, received all 3 vaccinations of mid-dose V503 in the Base Study and a fourth dose in the Extension Study within acceptable ranges, were seronegative at Day 1 and PCR negative from Day 1 to Month7 for the relevant HPV types, and had a Month 60 serum sample collected within an acceptable range.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Month 60: predose 4 in the Extension Study (Cohort 1)

| **End point values** | Mid-dose V503 (Cohort 1) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 150 | | | |
| Units: milli Merck U/mL | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Anti-HPV Type 6 (n=101) | 143.1 (117.9 to 173.7) | | | |
| Anti-HPV Type 11 (n=112) | 82.9 (68.1 to 100.9) | | | |
| Anti-HPV Type 16 (n=128) | 324.4 (266.7 to 394.7) | | | |
| Anti-HPV Type 18 (n=142) | 62.5 (49.5 to 78.9) | | | |
| Anti-HPV Type 31 (n=135) | 69.2 (56.6 to 84.4) | | | |
| Anti-HPV Type 33 (n=141) | 44.7 (37 to 54.1) | | | |
| Anti-HPV Type 45 (n=148) | 20.8 (17 to 25.5) | | | |
| Anti-HPV Type 52 (n=134) | 33.7 (27.6 to 41.1) | | | |
| Anti-HPV Type 58 (n=132) | 50.9 (40.9 to 63.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events information

Timeframe for reporting adverse events:

Base Study: SAEs up to Month (M) 7 (low- and high-dose V503) or up to M54 (mid-dose V503 and Gardasil); non-serious AEs up to Day 15 after vaccination. Cohort 1: SAEs M60 to 61; non-serious AEs up to Day 15 after vaccination 4. Cohort 2: SAEs M60 to 67.

Adverse event reporting additional description:

The analysis population included all participants who received >=1 vaccination and had safety follow-up.

Non-serious AEs were not solicited in Extension Cohort 2; however, some non-serious AEs were voluntarily reported.

| | |
|---|---|
| Assessment type | Systematic |

## Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

## Reporting groups

| | |
|---|---|
| Reporting group title | Base Study: Low-dose V503 |

Reporting group description:

V503 (9-Valent HPV Vaccine) low-dose 0.5 mL injection in a 3-dose regimen in the Base Study.

| | |
|---|---|
| Reporting group title | Base Study: Mid-dose V503 |

Reporting group description:

V503 mid-dose 0.5 mL injection in a 3-dose regimen in the Base Study.

| | |
|---|---|
| Reporting group title | Base Study: High-dose V503 |

Reporting group description:

V503 high-dose 0.5 mL injection in a 3-dose regimen in the Base Study.

| | |
|---|---|
| Reporting group title | Base Study: Gardasil |

Reporting group description:

Gardasil (4-Valent HPV Vaccine) 0.5 mL injection in a 3-dose regimen in the Base Study. Participants will be offered the V503 mid-dose 3-dose regimen in the extension study (Cohort 2).

| | |
|---|---|
| Reporting group title | Extension Study: Mid-dose V503 (Cohort 1) |

Reporting group description:

V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL fourth dose administration on Base Study participants who were randomized to receive a 3-dose regimen of V503 (9-Valent HPV) mid-dose 0.5 mL (Cohort 1).

| | |
|---|---|
| Reporting group title | Extension Study: Mid-dose V503 (Cohort 2) |

Reporting group description:

V503 (9-Valent HPV Vaccine) mid-dose 0.5 mL 3-dose regimen administration on Base Study participants who were randomized to receive a 3-dose regimen of Gardasil (4-Valent HPV Vaccine) (Cohort 2).

| Serious adverse events | Base Study: Low-dose V503 | Base Study: Mid-dose V503 | Base Study: High-dose V503 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 310 (1.29%) | 233 / 7071 (3.30%) | 5 / 305 (1.64%) |
| number of deaths (all causes) | 0 | 6 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Acute promyelocytic leukaemia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of the cervix | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ependymoma | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukaemic infiltration brain | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma in situ | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant palate neoplasm | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal cavity cancer | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory papilloma | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid cancer | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glioma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Axillary vein thrombosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 73 / 7071 (1.03%) | 2 / 305 (0.66%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 76 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 36 / 7071 (0.51%) | 1 / 305 (0.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 38 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous complete | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous incomplete | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Blighted ovum | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cephalo-pelvic disproportion | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 4 / 7071 (0.06%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix dystocia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| False labour | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal death | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 1 / 305 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 4 / 7071 (0.06%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal malposition | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal malpresentation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gestational diabetes | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labour complication | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oligohydramnios | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pre-eclampsia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 1 / 305 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature labour | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature rupture of membranes | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 4 / 7071 (0.06%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prolonged labour | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine contractions during pregnancy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Accidental death | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Allergy to vaccine | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Reproductive system and breast disorders** | | | |
| Bartholinitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical dysplasia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 5 / 7071 (0.07%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix haemorrhage uterine | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fallopian tube cyst | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vocal cord polyp | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Psychiatric disorders | | | |
| Anorexia and bulimia syndrome | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorexia nervosa | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 3 / 7071 (0.04%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Major depression | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Bladder injury | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burns second degree | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body in eye | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture displacement | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck injury | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Poisoning | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Spinal compression fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury cervical | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cleft lip and palate | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis Meckel's | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postural orthostatic tachycardia syndrome | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Benign intracranial hypertension | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic coma | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuritis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylitic myelopathy | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigeminal nerve disorder | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coeliac disease | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis ulcerative | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Omental infarction | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis of pregnancy | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Fibromyalgia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 310 (0.32%) | 9 / 7071 (0.13%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic inflammatory disease | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post abortion infection | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis streptococcal | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 2 / 7071 (0.03%) | 1 / 305 (0.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 310 (0.00%) | 0 / 7071 (0.00%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 310 (0.00%) | 1 / 7071 (0.01%) | 0 / 305 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Base Study: Gardasil | Extension Study: Mid-dose V503 (Cohort 1) | Extension Study: Mid-dose V503 (Cohort 2) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 184 / 7078 (2.60%) | 1 / 150 (0.67%) | 25 / 3049 (0.82%) |
| number of deaths (all causes) | 5 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute promyelocytic leukaemia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of the cervix | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ependymoma | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukaemic infiltration brain | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant palate neoplasm | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal cavity cancer | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian neoplasm | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pituitary tumour benign | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory papilloma | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glioma | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Axillary vein thrombosis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |

| | | | |
|---|---|---|---|
| Abortion induced | | | |
| subjects affected / exposed | 53 / 7078 (0.75%) | 0 / 150 (0.00%) | 3 / 3049 (0.10%) |
| occurrences causally related to treatment / all | 0 / 53 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 26 / 7078 (0.37%) | 0 / 150 (0.00%) | 8 / 3049 (0.26%) |
| occurrences causally related to treatment / all | 0 / 28 | 0 / 0 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous complete | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous incomplete | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blighted ovum | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cephalo-pelvic disproportion | | | |
| subjects affected / exposed | 6 / 7078 (0.08%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix dystocia | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| False labour | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal death | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal distress syndrome | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal malposition | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foetal malpresentation | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gestational diabetes | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labour complication | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oligohydramnios | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pre-eclampsia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature labour | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Premature rupture of membranes | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prolonged labour | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine contractions during pregnancy | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Accidental death | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Allergy to vaccine | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sarcoidosis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Bartholinitis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical dysplasia | | | |
| subjects affected / exposed | 3 / 7078 (0.04%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervix haemorrhage uterine | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fallopian tube cyst | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cyst | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal polyps | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vocal cord polyp | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anorexia and bulimia syndrome | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorexia nervosa | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bipolar disorder | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Major depression | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Bladder injury | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Burns second degree | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body in eye | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture displacement | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ligament rupture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck injury | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Poisoning | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord injury | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Spinal cord injury cervical | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ulna fracture | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cleft lip and palate | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis Meckel's | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Aortic valve incompetence | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postural orthostatic tachycardia syndrome | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Benign intracranial hypertension | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Diabetic coma | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Epilepsy | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paresis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersomnia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial venous sinus thrombosis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple sclerosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuritis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic intolerance | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sciatica | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylitic myelopathy | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tension headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigeminal nerve disorder | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Ear and labyrinth disorders** | | | |
| Vertigo positional | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Gastrointestinal disorders** | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coeliac disease | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Colitis ulcerative | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Omental infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis of pregnancy | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal colic | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Infections and infestations** | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 16 / 7078 (0.23%) | 0 / 150 (0.00%) | 2 / 3049 (0.07%) |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis infectious | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic fever | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic inflammatory disease | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post abortion infection | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis streptococcal | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 7078 (0.03%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 1 / 7078 (0.01%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 1 / 3049 (0.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 1 / 150 (0.67%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 7078 (0.00%) | 0 / 150 (0.00%) | 0 / 3049 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Base Study: Low-dose V503 | Base Study: Mid-dose V503 | Base Study: High-dose V503 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 278 / 310 (89.68%) | 6551 / 7071 (92.65%) | 280 / 305 (91.80%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 17 / 310 (5.48%) | 346 / 7071 (4.89%) | 11 / 305 (3.61%) |
| occurrences (all) | 20 | 405 | 13 |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 65 / 310 (20.97%) | 1879 / 7071 (26.57%) | 66 / 305 (21.64%) |
| occurrences (all) | 100 | 3071 | 106 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 100 / 310 (32.26%) | 2411 / 7071 (34.10%) | 91 / 305 (29.84%) |
| occurrences (all) | 157 | 3597 | 140 |
| Injection site pain | | | |
| subjects affected / exposed | 267 / 310 (86.13%) | 6360 / 7071 (89.94%) | 273 / 305 (89.51%) |
| occurrences (all) | 684 | 15383 | 672 |
| Injection site pruritus | | | |
| subjects affected / exposed | 18 / 310 (5.81%) | 389 / 7071 (5.50%) | 14 / 305 (4.59%) |
| occurrences (all) | 21 | 494 | 16 |
| Injection site swelling | | | |
| subjects affected / exposed | 100 / 310 (32.26%) | 2836 / 7071 (40.11%) | 103 / 305 (33.77%) |
| occurrences (all) | 154 | 4527 | 168 |
| Pyrexia | | | |
| subjects affected / exposed | 30 / 310 (9.68%) | 469 / 7071 (6.63%) | 17 / 305 (5.57%) |
| occurrences (all) | 35 | 563 | 19 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 22 / 310 (7.10%) | 513 / 7071 (7.25%) | 18 / 305 (5.90%) |
| occurrences (all) | 23 | 617 | 20 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 20 / 310 (6.45%) | 312 / 7071 (4.41%) | 12 / 305 (3.93%) |
| occurrences (all) | 22 | 343 | 12 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 310 (3.23%) | 376 / 7071 (5.32%) | 12 / 305 (3.93%) |
| occurrences (all) | 11 | 412 | 13 |

| **Non-serious adverse events** | Base Study: Gardasil | Extension Study: Mid-dose V503 (Cohort 1) | Extension Study: Mid-dose V503 (Cohort 2) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6268 / 7078 (88.56%) | 130 / 150 (86.67%) | 89 / 3049 (2.92%) |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 307 / 7078 (4.34%) | 0 / 150 (0.00%) | 2 / 3049 (0.07%) |
| occurrences (all) | 368 | 0 | 2 |
| Headache | | | |
| subjects affected / exposed | 1756 / 7078 (24.81%) | 32 / 150 (21.33%) | 11 / 3049 (0.36%) |
| occurrences (all) | 2788 | 41 | 13 |
| General disorders and administration site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 1810 / 7078 (25.57%) | 33 / 150 (22.00%) | 9 / 3049 (0.30%) |
| occurrences (all) | 2564 | 34 | 9 |
| Injection site pain | | | |
| subjects affected / exposed | 5911 / 7078 (83.51%) | 124 / 150 (82.67%) | 59 / 3049 (1.94%) |
| occurrences (all) | 13001 | 128 | 94 |
| Injection site pruritus | | | |
| subjects affected / exposed | 282 / 7078 (3.98%) | 1 / 150 (0.67%) | 1 / 3049 (0.03%) |
| occurrences (all) | 341 | 1 | 1 |
| Injection site swelling | | | |
| subjects affected / exposed | 2035 / 7078 (28.75%) | 49 / 150 (32.67%) | 12 / 3049 (0.39%) |
| occurrences (all) | 2988 | 51 | 12 |
| Pyrexia | | | |
| subjects affected / exposed | 463 / 7078 (6.54%) | 6 / 150 (4.00%) | 7 / 3049 (0.23%) |
| occurrences (all) | 550 | 6 | 7 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 459 / 7078 (6.48%) | 2 / 150 (1.33%) | 4 / 3049 (0.13%) |
| occurrences (all) | 551 | 2 | 4 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 296 / 7078 (4.18%) | 4 / 150 (2.67%) | 5 / 3049 (0.16%) |
| occurrences (all) | 314 | 5 | 5 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 389 / 7078 (5.50%) | 1 / 150 (0.67%) | 0 / 3049 (0.00%) |
| occurrences (all) | 420 | 1 | 0 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 November 2008 | Amendment 1: Revised the primary objective and hypothesis for measuring efficacy of the V503 vaccine against infection and disease caused by HPV Types 31, 33, 45, 52, and 58. |
| 18 August 2011 | Amendment 2: Updated the data analysis related to the secondary objective pertaining to reduction in combined incidence of HPV Types 31, 33, 45, 52, and 58-related persistent infection. Specifically, the statistical criterion for success relating to the lower bound of the 95% confidence interval was changed from 0% to 25%. |
| 04 May 2012 | Amendment 3: Added two study visits, Month 48 and Month 54, to help ensure that an adequate number of primary efficacy endpoints were accrued to perform the primary efficacy analysis before the study ended. |
| 14 October 2013 | Amendment 4: Added an extension to the V503-001 Base Study, with the goals to 1) assess whether immunogenicity of a fourth dose of V503 vaccine shows evidence of immune memory, and 2) to offer a 3-dose regimen of V503 vaccine to participants in the control arm of the study. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported