



Clinical trial results:

A randomised, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer

Summary

| | |
|--------------------------|--|
| EudraCT number | 2006-000562-36 |
| Trial protocol | IE HU FR GB SK EE CZ DK BE DE GR NL IT ES SI BG AT |
| Global end of trial date | 01 July 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v2 (current) |
| This version publication date | 06 April 2025 |
| First version publication date | 02 July 2022 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLAP016B2301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00490139 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 July 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare disease-free survival (DFS) in patients with Human Epidermal Growth Factor Receptor 2 (HER2) overexpressing and/or amplified breast cancer randomized to trastuzumab for one year (Trastuzumab arm) versus lapatinib for one year (Lapatinib arm; this arm was discontinued prior to the primary analysis due to futility) versus weekly trastuzumab (12 or 18 weeks, according to assigned design) followed by a six-week washout period followed by lapatinib (28 or 34 weeks, according to assigned design; Trastuzumab followed by Lapatinib arm) versus trastuzumab in combination with lapatinib for one year (Lapatinib plus Trastuzumab arm).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 16 May 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 | Argentina: 64 |
| Country: Number of subjects enrolled | Australia: 181 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 231 |
| Country: Number of subjects enrolled | Brazil: 98 |
| Country: Number of subjects enrolled | Bulgaria: 26 |
| Country: Number of subjects enrolled | Canada: 42 |
| Country: Number of subjects enrolled | Chile: 108 |
| Country: Number of subjects enrolled | China: 441 |
| Country: Number of subjects enrolled | Czechia: 116 |
| Country: Number of subjects enrolled | Denmark: 187 |
| Country: Number of subjects enrolled | Estonia: 4 |
| Country: Number of subjects enrolled | France: 410 |
| Country: Number of subjects enrolled | Germany: 1375 |
| Country: Number of subjects enrolled | Greece: 56 |
| Country: Number of subjects enrolled | Hong Kong: 56 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Hungary: 134 |
| Country: Number of subjects enrolled | India: 201 |
| Country: Number of subjects enrolled | Ireland: 52 |
| Country: Number of subjects enrolled | Israel: 47 |
| Country: Number of subjects enrolled | Italy: 371 |
| Country: Number of subjects enrolled | Japan: 142 |
| Country: Number of subjects enrolled | Korea, Republic of: 353 |
| Country: Number of subjects enrolled | Mexico: 31 |
| Country: Number of subjects enrolled | Netherlands: 87 |
| Country: Number of subjects enrolled | New Zealand: 41 |
| Country: Number of subjects enrolled | Norway: 40 |
| Country: Number of subjects enrolled | Pakistan: 204 |
| Country: Number of subjects enrolled | Peru: 143 |
| Country: Number of subjects enrolled | Philippines: 150 |
| Country: Number of subjects enrolled | Poland: 176 |
| Country: Number of subjects enrolled | Romania: 105 |
| Country: Number of subjects enrolled | Russian Federation: 324 |
| Country: Number of subjects enrolled | Singapore: 25 |
| Country: Number of subjects enrolled | Slovakia: 53 |
| Country: Number of subjects enrolled | Slovenia: 20 |
| Country: Number of subjects enrolled | South Africa: 168 |
| Country: Number of subjects enrolled | Spain: 267 |
| Country: Number of subjects enrolled | Switzerland: 56 |
| Country: Number of subjects enrolled | Taiwan: 374 |
| Country: Number of subjects enrolled | Thailand: 172 |
| Country: Number of subjects enrolled | Ukraine: 85 |
| Country: Number of subjects enrolled | United Kingdom: 243 |
| Country: Number of subjects enrolled | United States: 917 |
| Worldwide total number of subjects | 8381 |
| EEA total number of subjects | 3715 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 7526 |
| From 65 to 84 years | 855 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 969 centers in 44 countries worldwide.

Pre-assignment

Screening details:

Based on the IDMC results from 18 August 2011, any patient enrolled onto Lapatinib arm were considered for a new treatment strategy based on discussion with their physician.

Period 1

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

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Lapatinib plus Trastuzumab |

Arm description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lapatinib (OL) 1000 milligrams (mg) daily with trastuzumab (tras) (8 milligrams per kilogram [mg/kg] intravenous [IV] loading dose [LD], followed by 6 mg/kg IV every 3 weeks [E3W]) for 52 weeks (wks). * Design 2: OL 750 mg daily plus wkly tras (4 mg/kg LD, followed by 2 mg/kg IV) concomitantly (conc.) with wkly paclitaxel (pac) 80 mg per squared meter (mg/m²) IV or docetaxel (doc) 75 mg/m² IV E3W for 12 wks. After completion of pac or doc, par. received OL at an increased dose of 1000 mg daily in combination with tras (6 mg/kg without a LD) E3W for 40 wks. * Design 2B: OL 750 mg plus wkly tras (4 mg/kg IV LD, followed by 2 mg/kg IV wkly) conc. with doc 75 mg/m² E3W and carboplatin (carb) AUC6 IV for 18 wks. After completion of doc and carb, par. received tras E3W (6 mg/kg without a LD) plus OL 1000 mg daily for 34 wks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Design 1: Oral lapatinib 1000 mg daily concurrent with trastuzumab 8 mg/kg IV loading dose followed by 6mg/kg IV every 3 weeks (52 weeks total). Design 2: Trastuzumab (4mg/kg loading dose followed by 2mg/kg IV weekly) concurrent with oral lapatinib 750 mg daily and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles (12 weeks). After completion of chemotherapy, the dose of lapatinib will be increased to 1000mg daily concurrently with trastuzumab every 3 weeks (6mg/kg without loading dose) for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concurrently with oral lapatinib 750mg plus weekly trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV. After the completion of chemotherapy, trastuzumab will be administered every 3 weeks (6mg/kg without loading dose) concurrent with lapatinib 1000mg daily for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Trastuzumab (4mg/kg loading dose followed by 2mg/kg IV weekly) concurrent with oral lapatinib 750 mg daily and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m²

every 21 days for 4 cycles (12 weeks). After completion of chemotherapy, the dose of lapatinib will be increased to 1000mg daily concurrently with trastuzumab every 3 weeks (6mg/kg without loading dose) for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concurrently with oral lapatinib 750mg plus weekly trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV. After the completion of chemotherapy, trastuzumab will be administered every 3 weeks (6mg/kg without loading dose) concurrent with lapatinib 1000mg daily for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Trastuzumab (4mg/kg loading dose followed by 2mg/kg IV weekly) concurrent with oral lapatinib 750 mg daily and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles (12 weeks). After completion of chemotherapy, the dose of lapatinib will be increased to 1000mg daily concurrently with trastuzumab every 3 weeks (6mg/kg without loading dose) for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 1: Oral lapatinib 1000 mg daily concurrent with trastuzumab 8 mg/kg IV loading dose followed by 6mg/kg IV every 3 weeks (52 weeks total). Design 2: Trastuzumab (4mg/kg loading dose followed by 2mg/kg IV weekly) concurrent with oral lapatinib 750 mg daily and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles (12 weeks). After completion of chemotherapy, the dose of lapatinib will be increased to 1000mg daily concurrently with trastuzumab every 3 weeks (6mg/kg without loading dose) for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concurrently with oral lapatinib 750mg plus weekly trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV. After the completion of chemotherapy, trastuzumab will be administered every 3 weeks (6mg/kg without loading dose) concurrent with lapatinib 1000mg daily for an additional 40 weeks (52 weeks total).

| | |
|------------------|-----------------------------------|
| Arm title | Trastuzumab followed by Lapatinib |
|------------------|-----------------------------------|

Arm description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: weekly tras for 12 weeks (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly), followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks for 12 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2B: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV for 18 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 28 weeks.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 1: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total). Design 2: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks administered concomitantly and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles; followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) followed by a 6 week treatment-free interval followed by

oral lapatinib 1500 mg daily for 28 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks administered concomitantly and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles; followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) followed by a 6 week treatment-free interval followed by oral lapatinib 1500 mg daily for 28 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks administered concomitantly and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles; followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total).

| | |
|--|-----------|
| Investigational medicinal product name | Lapatinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Design 1: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total). Design 2: Trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) for 12 weeks administered concomitantly and either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² every 21 days for 4 cycles; followed by a 6 week treatment-free interval followed by oral lapatinib 1500mg daily for 34 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with trastuzumab (4mg/kg IV loading dose followed by 2mg/kg IV weekly) followed by a 6 week treatment-free interval followed by oral lapatinib 1500 mg daily for 28 weeks (52 weeks total).

| | |
|------------------|-----------|
| Arm title | Lapatinib |
|------------------|-----------|

Arm description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lap 1500 mg daily for 52 weeks. * Design 2: oral lap 750 mg daily concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received oral lap at an increased dose of 1500 mg daily for 40 weeks. * Design 2B: oral lap 750 mg daily concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, oral lap was given at an increased dose of 1500 mg for 34 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lapatinid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Design 1: Lapatinib 1500mg oral daily for a total of 52 weeks. Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with oral lapatinib at 750mg daily. After completion of chemotherapy, oral lapatinib administered at 1500mg daily for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and

carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with oral lapatinib at 750mg daily. After completion of chemotherapy, the dose of lapatinib will be increased to 1500mg oral daily for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with oral lapatinib at 750mg daily. After completion of chemotherapy, oral lapatinib administered at 1500mg daily for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with oral lapatinib at 750mg daily. After completion of chemotherapy, the dose of lapatinib will be increased to 1500mg oral daily for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with oral lapatinib at 750mg daily. After completion of chemotherapy, oral lapatinib administered at 1500mg daily for an additional 40 weeks (52 weeks total).

| | |
|------------------|-------------|
| Arm title | Trastuzumab |
|------------------|-------------|

Arm description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: tras 8 mg/kg IV LD, followed by 6 mg/kg IV every 3 weeks for 52 weeks. * Design 2: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received tras (6 mg/kg without a LD every 3 weeks for 40 weeks. * Design 2B: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, participants received tras every 3 weeks (6 mg/kg without a LD) for 34 weeks. "

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 1: Trastuzumab 8mg/kg IV loading dose followed by 6mg/kg IV every 3 weeks for a total of 52 weeks. Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with trastuzumab 4mg/kg IV loading dose followed by 2mg/kg IV weekly. After completion of chemotherapy, trastuzumab administered every 3 weeks (6mg/kg IV without loading dose) for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with trastuzumab 4mg/kg IV loading dose followed by 2mg/kg IV weekly. After completion of chemotherapy, trastuzumab (6mg/kg without loading dose) every 3 weeks for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with trastuzumab 4mg/kg IV loading dose followed by 2mg/kg IV weekly. After completion of chemotherapy, trastuzumab administered every 3 weeks (6mg/kg IV

without loading dose) for an additional 40 weeks (52 weeks total). Design 2B: Docetaxel 75mg/m² and carboplatin AUC 6 every 3 weeks for 6 cycles (18 weeks) administered concomitantly with trastuzumab 4mg/kg IV loading dose followed by 2mg/kg IV weekly. After completion of chemotherapy, trastuzumab (6mg/kg without loading dose) every 3 weeks for an additional 40 weeks (52 weeks total).

| | |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Design 2: Either paclitaxel 80mg/m² IV weekly for 12 weeks OR docetaxel 75mg/m² IV every 3 weeks for 4 cycles administered concomitantly with trastuzumab 4mg/kg IV loading dose followed by 2mg/kg IV weekly. After completion of chemotherapy, trastuzumab administered every 3 weeks (6mg/kg IV without loading dose) for an additional 40 weeks (52 weeks total).

| Number of subjects in period 1 | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib |
|--|----------------------------|-----------------------------------|-----------|
| Started | 2093 | 2091 | 2100 |
| Safety population | 2061 | 2076 | 2056 |
| Completed | 1132 | 1184 | 1179 |
| Not completed | 961 | 907 | 921 |
| Consent withdrawn by subject | 333 | 322 | 396 |
| Data unavailable due to regulatory issues | 98 | 96 | 85 |
| Data unavailable due to lapsed ethical consent | 14 | 13 | 14 |
| Patient did not sign ICF 12 | 169 | 176 | 139 |
| Lost to follow-up | 249 | 216 | 205 |
| Other reasons as defined per protocol | 98 | 84 | 82 |

| Number of subjects in period 1 | Trastuzumab |
|--|-------------|
| Started | 2097 |
| Safety population | 2076 |
| Completed | 1192 |
| Not completed | 905 |
| Consent withdrawn by subject | 295 |
| Data unavailable due to regulatory issues | 95 |
| Data unavailable due to lapsed ethical consent | 14 |
| Patient did not sign ICF 12 | 167 |
| Lost to follow-up | 229 |
| Other reasons as defined per protocol | 105 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Lapatinib plus Trastuzumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lapatinib (OL) 1000 milligrams (mg) daily with trastuzumab (tras) (8 milligrams per kilogram [mg/kg] intravenous [IV] loading dose [LD], followed by 6 mg/kg IV every 3 weeks [E3W]) for 52 weeks (wks). * Design 2: OL 750 mg daily plus wkly tras (4 mg/kg LD, followed by 2 mg/kg IV) concomitantly (conc.) with wkly paclitaxel (pac) 80 mg per squared meter (mg/m²) IV or docetaxel (doc) 75 mg/m² IV E3W for 12 wks. After completion of pac or doc, par. received OL at an increased dose of 1000 mg daily in combination with tras (6 mg/kg without a LD) E3W for 40 wks. * Design 2B: OL 750 mg plus wkly tras (4 mg/kg IV LD, followed by 2 mg/kg IV wkly) conc. with doc 75 mg/m² E3W and carboplatin (carb) AUC6 IV for 18 wks. After completion of doc and carb, par. received tras E3W (6 mg/kg without a LD) plus OL 1000 mg daily for 34 wks.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Trastuzumab followed by Lapatinib |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: weekly tras for 12 weeks (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly), followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks for 12 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2B: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV for 18 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 28 weeks.

| | |
|-----------------------|-----------|
| Reporting group title | Lapatinib |
|-----------------------|-----------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lap 1500 mg daily for 52 weeks. * Design 2: oral lap 750 mg daily concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received oral lap at an increased dose of 1500 mg daily for 40 weeks. * Design 2B: oral lap 750 mg daily concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, oral lap was given at an increased dose of 1500 mg for 34 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Trastuzumab |
|-----------------------|-------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: tras 8 mg/kg IV LD, followed by 6 mg/kg IV every 3 weeks for 52 weeks. * Design 2: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received tras (6 mg/kg without a LD) every 3 weeks for 40 weeks. * Design 2B: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, participants received tras every 3 weeks (6 mg/kg without a LD) for 34 weeks. "

| Reporting group values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib |
|--|----------------------------|-----------------------------------|-----------|
| Number of subjects | 2093 | 2091 | 2100 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |

| | | | |
|--|------|------|------|
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 1879 | 1877 | 1889 |
| From 65-84 years | 214 | 214 | 211 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2091 | 2086 | 2098 |
| Male | 2 | 5 | 2 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 48 | 45 | 47 |
| Asian: Central/South | 107 | 103 | 110 |
| Asian: East | 311 | 312 | 299 |
| Asian: Japanese | 33 | 36 | 33 |
| Asian: South East | 95 | 92 | 107 |
| Black or African American | 38 | 30 | 43 |
| Native Hawaiian or Other Pacific | 2 | 4 | 4 |
| White: Arabic | 53 | 52 | 62 |
| White: Caucasian | 1392 | 1402 | 1372 |
| Other Race | 14 | 14 | 23 |
| Unknown/Missing | 0 | 1 | 0 |
| Axillary Lymph Node Status | | | |
| Axillary Lymph Node Status was categorized as: a) Not applicable (neoadjuvant chemotherapy); b) Node negative (no neoadjuvant chemotherapy); c) 1-3 positive nodes (no neoadjuvant chemotherapy); d) >= 4 positive nodes (no neoadjuvant chemotherapy) | | | |
| Units: Subjects | | | |
| Not applicable (neoadjuvant chemotherapy) | 168 | 170 | 167 |
| Node negative (no neoadjuvant chemotherapy) | 845 | 842 | 841 |
| 1-3 positive nodes (no neoadjuvant chemotherapy) | 617 | 617 | 620 |
| >= 4 positive nodes (no neoadjuvant chemotherapy) | 463 | 462 | 472 |
| Timing of Chemotherapy | | | |
| Timing of (neo)adjuvant chemotherapy was defined as follows: Design 1 – sequentially (all chemotherapy completed prior to randomization) versus Design 2 – concurrently with targeted therapy (taxane medication administered with targeted treatment after randomization). Subjects treated concurrently but without anthracycline (Design 2B) were regarded as part of Design 2 for all stratified analyses. | | | |
| Units: Subjects | | | |
| Sequential | 1155 | 1143 | 1168 |
| Concurrent | 938 | 948 | 932 |
| Hormone Receptor (HR) Status | | | |
| HR status was determined from the percentage of Estrogen Receptor (ER) and Progesterone Receptor (PgR) cells stained positive: a) Positive: if the percentage of cells stained positive is >= 1% for either ER or PgR; b) Negative: if the percentage of cells stained positive is < 1% for both ER and PgR | | | |
| Units: Subjects | | | |
| Negative | 890 | 886 | 903 |
| Positive | 1203 | 1205 | 1197 |
| GenderNIH | | | |
| Units: Subjects | | | |
| Female | 2091 | 2086 | 2098 |
| Male | 2 | 5 | 2 |

| | | | |
|--|-----------------|-----------------|-----------------|
| AgeContinuous Units: years arithmetic mean standard deviation | 50.9 ± 10.23 | 50.8 ± 10.32 | 51.2 ± 10.18 |
|--|-----------------|-----------------|-----------------|

| Reporting group values | Trastuzumab | Total | |
|--|-------------|-------|--|
| Number of subjects | 2097 | 8381 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 1881 | 7526 | |
| From 65-84 years | 216 | 855 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 2097 | 8372 | |
| Male | 0 | 9 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 47 | 187 | |
| Asian: Central/South | 109 | 429 | |
| Asian: East | 314 | 1236 | |
| Asian: Japanese | 43 | 145 | |
| Asian: South East | 89 | 383 | |
| Black or African American | 25 | 136 | |
| Native Hawaiian or Other Pacific | 5 | 15 | |
| White: Arabic | 69 | 236 | |
| White: Caucasian | 1382 | 5548 | |
| Other Race | 14 | 65 | |
| Unknown/Missing | 0 | 1 | |
| Axillary Lymph Node Status | | | |
| Axillary Lymph Node Status was categorized as: a) Not applicable (neoadjuvant chemotherapy); b) Node negative (no neoadjuvant chemotherapy); c) 1-3 positive nodes (no neoadjuvant chemotherapy); d) >= 4 positive nodes (no neoadjuvant chemotherapy) | | | |
| Units: Subjects | | | |
| Not applicable (neoadjuvant chemotherapy) | 181 | 686 | |
| Node negative (no neoadjuvant chemotherapy) | 844 | 3372 | |
| 1-3 positive nodes (no neoadjuvant chemotherapy) | 603 | 2457 | |
| >= 4 positive nodes (no neoadjuvant chemotherapy) | 469 | 1866 | |
| Timing of Chemotherapy | | | |
| Timing of (neo)adjuvant chemotherapy was defined as follows: Design 1 – sequentially (all chemotherapy completed prior to randomization) versus Design 2 – concurrently with targeted therapy (taxane medication administered with targeted treatment after randomization). Subjects treated concurrently but without anthracycline (Design 2B) were regarded as part of Design 2 for all stratified | | | |

| | | | |
|---|-------------|------|--|
| analyses. | | | |
| Units: Subjects | | | |
| Sequential | 1147 | 4613 | |
| Concurrent | 950 | 3768 | |
| Hormone Receptor (HR) Status | | | |
| HR status was determined from the percentage of Estrogen Receptor (ER) and Progesterone Receptor (PgR) cells stained positive: a) Positive: if the percentage of cells stained positive is $\geq 1\%$ for either ER or PgR; b) Negative: if the percentage of cells stained positive is $< 1\%$ for both ER and PgR | | | |
| Units: Subjects | | | |
| Negative | 897 | 3576 | |
| Positive | 1200 | 4805 | |
| GenderNIH | | | |
| Units: Subjects | | | |
| Female | 2097 | 8372 | |
| Male | 0 | 9 | |
| AgeContinuous | | | |
| Units: years | | | |
| arithmetic mean | 51.0 | | |
| standard deviation | ± 10.25 | - | |

End points

End points reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Lapatinib plus Trastuzumab |
|-----------------------|----------------------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lapatinib (OL) 1000 milligrams (mg) daily with trastuzumab (tras) (8 milligrams per kilogram [mg/kg] intravenous [IV] loading dose [LD], followed by 6 mg/kg IV every 3 weeks [E3W]) for 52 weeks (wks). * Design 2: OL 750 mg daily plus wkly tras (4 mg/kg LD, followed by 2 mg/kg IV) concomitantly (conc.) with wkly paclitaxel (pac) 80 mg per squared meter (mg/m²) IV or docetaxel (doc) 75 mg/m² IV E3W for 12 wks. After completion of pac or doc, par. received OL at an increased dose of 1000 mg daily in combination with tras (6 mg/kg without a LD) E3W for 40 wks. * Design 2B: OL 750 mg plus wkly tras (4 mg/kg IV LD, followed by 2 mg/kg IV wkly) conc. with doc 75 mg/m² E3W and carboplatin (carb) AUC6 IV for 18 wks. After completion of doc and carb, par. received tras E3W (6 mg/kg without a LD) plus OL 1000 mg daily for 34 wks.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Trastuzumab followed by Lapatinib |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: weekly tras for 12 weeks (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly), followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks for 12 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 34 weeks. * Design 2B: weekly tras (4 mg/kg IV loading dose, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV for 18 weeks, followed by a 6-week washout period, followed by oral lap 1500 mg daily for 28 weeks.

| | |
|-----------------------|-----------|
| Reporting group title | Lapatinib |
|-----------------------|-----------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: oral lap 1500 mg daily for 52 weeks. * Design 2: oral lap 750 mg daily concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received oral lap at an increased dose of 1500 mg daily for 40 weeks. * Design 2B: oral lap 750 mg daily concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, oral lap was given at an increased dose of 1500 mg for 34 weeks.

| | |
|-----------------------|-------------|
| Reporting group title | Trastuzumab |
|-----------------------|-------------|

Reporting group description:

Participants received treatment per one of three designs and adjuvant radiotherapy / adjuvant anti-estrogen therapy when clinically indicated. * Design 1: tras 8 mg/kg IV LD, followed by 6 mg/kg IV every 3 weeks for 52 weeks. * Design 2: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with weekly paclitaxel 80 mg/m² IV or docetaxel 75 mg/m² IV every 3 weeks, for 12 weeks. After completion of paclitaxel or docetaxel, participants received tras (6 mg/kg without a LD) every 3 weeks for 40 weeks. * Design 2B: weekly tras (4 mg/kg IV LD, followed by 2 mg/kg IV weekly) concomitantly with docetaxel 75 mg/m² every 3 weeks and carboplatin AUC6 IV, for 18 weeks. After completion of docetaxel and carboplatin, participants received tras every 3 weeks (6 mg/kg without a LD) for 34 weeks. "

Primary: Disease-Free Survival (DFS) at the Primary Analysis

| | |
|-----------------|---|
| End point title | Disease-Free Survival (DFS) at the Primary Analysis |
|-----------------|---|

End point description:

Disease-Free Survival (DFS) was defined as the interval between randomization and the date of first occurrence of disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer or death without recurrence. Only deaths occurring in participants whose clinical follow-up was ongoing at the time of death and who had no recurrence, contralateral breast cancer (CBC) or second primary malignancy (SPM) reported prior to death were considered as death without recurrence. DFS was estimated using the Kaplan Meier method. The percentile data values presented here indicate the percentage (95, 90, 85, 80 and 75 percent) of participants who had disease free survival for the indicated years.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| From randomization until the date of the first occurrence of disease recurrence, a contralateral invasive breast cancer, a second primary cancer, or death from any cause (median follow-up of 4.5 years) | |

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 2100 | 2097 |
| Units: Years | | | | |
| number (not applicable) | | | | |
| 95th Percentile | 1.9 | 1.3 | 1.0 | 1.5 |
| 90th Percentile | 3.2 | 2.8 | 1.8 | 2.6 |
| 85th Percentile | 5.1 | 4.8 | 2.8 | 4.2 |
| 80th Percentile | 6.1 | 999 | 999 | 5.6 |
| 75th Percentile | 6.1 | 999 | 999 | 999 |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | DFS at the Primary Analysis |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.61 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.13 |

| | |
|---|--|
| Statistical analysis title | DFS at the Primary Analysis |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.048 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.84 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1 |

Secondary: Disease-Free Survival (DFS) at the 10-Year Follow-Up

| | |
|-----------------|--|
| End point title | Disease-Free Survival (DFS) at the 10-Year Follow-Up |
|-----------------|--|

End point description:

Disease-Free Survival (DFS) was defined as the interval between randomization and the date of first occurrence of disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer or death without recurrence. Only deaths occurring in participants whose clinical follow-up was ongoing at the time of death and who had no recurrence, contralateral breast cancer (CBC) or second primary malignancy (SPM) reported prior to death were considered as death without recurrence. DFS was estimated using the Kaplan

Meier method. The percentile data values presented here indicate the percentage (95, 90, 85 and 80 percent) of participants who had disease free survival for the indicated years.

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

End point timeframe:

From randomization until the date of the first occurrence of disease recurrence, a contralateral invasive breast cancer, a second primary cancer, or death from any cause, assessed up to approximately 10 years

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[1] | 2097 |
| Units: Years | | | | |
| number (not applicable) | | | | |
| 95th Percentile | 1.89 | 1.27 | | 1.49 |
| 90th Percentile | 3.21 | 2.80 | | 2.63 |
| 85th Percentile | 5.92 | 4.85 | | 4.43 |
| 80th Percentile | 8.99 | 9.18 | | 7.42 |

Notes:

[1] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | DFS at the 10-Year Follow-Up |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.914 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.05 |

| | |
|---|--|
| Statistical analysis title | DFS at the 10-Year Follow-Up |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.887 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.02 |

Secondary: Overall Survival (OS) at the Primary Analysis

| | |
|-----------------|---|
| End point title | Overall Survival (OS) at the Primary Analysis |
|-----------------|---|

End point description:

Overall Survival (OS) was defined as the time from randomization until death due to any cause. Participants who had not died were censored at the last date they were known to be alive, or date of withdrawal of consent. OS was calculated in years as (date of death minus the date of randomization +1) divided by 365.25. The percentile data values presented here indicate the percentage (99, 98, 97, 96, 95 and 90 percent) of participants who survived for the indicated years.

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

End point timeframe:

From randomization until death due to any cause (median follow-up of 4.5 years)

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[2] | 2097 |
| Units: Years | | | | |
| number (not applicable) | | | | |
| 99th Percentile | 1.7 | 1.2 | | 1.7 |
| 98th Percentile | 2.2 | 1.6 | | 2.1 |
| 97th Percentile | 2.8 | 2.2 | | 2.6 |
| 96th Percentile | 3.4 | 2.9 | | 3.0 |
| 95th Percentile | 3.9 | 3.7 | | 3.6 |
| 90th Percentile | 999 | 999 | | 5.9 |

Notes:

[2] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | OS at the Primary Analysis |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.433 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.16 |

| | |
|---|--|
| Statistical analysis title | OS at the Primary Analysis |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.078 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.62 |
| upper limit | 1.03 |

Secondary: Overall Survival (OS) at the 10-Year Follow-Up

| | |
|--|--|
| End point title | Overall Survival (OS) at the 10-Year Follow-Up |
| End point description: | |
| Overall Survival (OS) was defined as the time from randomization until death due to any cause. Participants who had not died were censored at the last date they were known to be alive, or date of withdrawal of consent. OS was calculated in years as (date of death minus the date of randomization +1) divided by 365.25. The percentile data values presented here indicate the percentage (99, 98, 95 and 90 percent) of participants who survived for the indicated years. | |
| End point type | Secondary |

End point timeframe:

From randomization until death due to any cause, assessed up to approximately 10 years

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[3] | 2097 |
| Units: Years | | | | |
| number (not applicable) | | | | |
| 99th Percentile | 1.68 | 1.17 | | 1.75 |
| 98th Percentile | 2.19 | 1.60 | | 2.07 |
| 95th Percentile | 3.92 | 3.52 | | 3.65 |
| 90th Percentile | 8.31 | 8.49 | | 6.72 |

Notes:

[3] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | OS at the 10-Year Follow-Up |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.863 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.04 |

| | |
|---|--|
| Statistical analysis title | OS at the 10-Year Follow-Up |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.853 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.03 |

Secondary: Analysis of Time to Distant Recurrence (TTDR)

| | |
|-----------------|---|
| End point title | Analysis of Time to Distant Recurrence (TTDR) |
|-----------------|---|

End point description:

Time to Distant Recurrence (TTDR) was defined as the the time from randomization to first distant breast cancer recurrence, ignoring locoregional recurrences and second primary cancers, (including contralateral breast cancers and non-breast second malignancies) and counting deaths without recurrence as a competing risk.

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

End point timeframe:

From randomization until the date of the first occurrence of distant recurrence, assessed up to approximately 10 years

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[4] | 2097 |
| Units: Participants | | | | |
| Distant recurrence | 213 | 238 | | 250 |
| Death as a competing risk | 45 | 41 | | 54 |
| Censored | 1835 | 1812 | | 1793 |

Notes:

[4] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to Distant Recurrence (TTDR) |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.968 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.16 |

| | |
|----------------------------|--|
| Statistical analysis title | Time to Distant Recurrence (TTDR) |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |

| | |
|---|-------------------|
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.852 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.02 |

Secondary: Analysis of Time to Recurrence (TTR)

| | |
|--|--------------------------------------|
| End point title | Analysis of Time to Recurrence (TTR) |
| End point description: | |
| Time to Recurrence (TTR) was defined as the the time from randomization to breast cancer recurrence, ignoring second primary cancers (including contralateral breast cancers and non-breast second malignancies) and counting deaths without recurrence as a competing risk. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until the date of the first occurrence of a disease recurrence, assessed up to approximately 10 years | |

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|--|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[5] | 2097 |
| Units: Participants | | | | |
| Local, regional, or distant recurrence | 243 | 275 | | 298 |
| Death as a competing risk | 43 | 38 | | 46 |
| Censored | 1807 | 1778 | | 1753 |

Notes:

[5] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to Recurrence (TTR) |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.1 |

| | |
|---|--|
| Statistical analysis title | Time to Recurrence (TTR) |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.811 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 0.96 |

Secondary: Analysis of Time to Central Nervous System (CNS) Recurrence

| | |
|---|---|
| End point title | Analysis of Time to Central Nervous System (CNS) Recurrence |
| End point description: | |
| Time to Central Nervous System (CNS) recurrence was defined as the time from randomization to first CNS recurrence. Both brain metastasis and meningitis carcinomatosa were considered. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until the first central nervous system recurrence, assessed up to approximately 10 years | |

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[6] | 2097 |
| Units: Participants | | | | |
| CNS recurrence | 91 | 91 | | 95 |
| Death as a competing risk | 114 | 117 | | 142 |
| Censored | 1888 | 1883 | | 1860 |

Notes:

[6] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to CNS Recurrence |
| Comparison groups | Trastuzumab followed by Lapatinib v Trastuzumab |
| Number of subjects included in analysis | 4188 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.31 |

| | |
|---|--|
| Statistical analysis title | Time to CNS Recurrence |
| Comparison groups | Lapatinib plus Trastuzumab v Trastuzumab |
| Number of subjects included in analysis | 4190 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.986 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.31 |

Secondary: Cumulative incidence of brain metastases

| | |
|---|--|
| End point title | Cumulative incidence of brain metastases |
| End point description: | |
| <p>The cumulative incidence of brain metastases as the first site of breast cancer recurrence among treatment arms was assessed using a hierarchy of primary type and location of first DFS event in cases where more than one event was identified simultaneously. Because diagnostic procedures for different types of recurrence could not be performed on exactly the same day, any diagnoses noted within a two month (60 day) period of the first reported event was considered as identified simultaneously for purposes of defining the type of the first event and the date of event was be regarded as the earliest of the relevant events.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| <p>From randomization until the date of the first occurrence of a disease recurrence, assessed up to approximately 10 years</p> | |

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 0 ^[7] | 2097 |
| Units: Participants | 50 | 52 | | 48 |

Notes:

[7] - The Lapatinib alone arm was discontinued prior to primary analysis due to futility.

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

| | |
|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

Pre-treatment deaths were collected from day of participant's informed consent to the day before first dose of study medication.

On-treatment deaths were collected from first dose of study medication to 30 days after last dose of study medication (on-treatment), up to approximately 56 weeks.

Deaths were collected in the post treatment survival follow up from 31 days after last dose of study medication until the end of the study, up to approximately 10 years.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pre-treatment deaths: Up to 14 days prior to treatment. On-treatment deaths: Up to 56 weeks. Post-treatment deaths: up to 10 years.

| End point values | Lapatinib plus Trastuzumab | Trastuzumab followed by Lapatinib | Lapatinib | Trastuzumab |
|-----------------------------|----------------------------|-----------------------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2093 | 2091 | 2100 | 2097 |
| Units: Participants | | | | |
| Pre-treatment deaths | 1 | 2 | 1 | 2 |
| On-treatment deaths | 6 | 5 | 12 | 3 |
| Post-treatment deaths | 189 | 190 | 250 | 228 |
| All deaths | 196 | 197 | 263 | 233 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from first dose of study medication until the last dose plus 30 days post-treat follow-up, assessed up to approximately 56 weeks.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Lapatinib plus Trastuzumab |
|-----------------------|----------------------------|

Reporting group description:

Lapatinib plus Trastuzumab: Events up to 30 days post-treatment

| | |
|-----------------------|-----------|
| Reporting group title | Lapatinib |
|-----------------------|-----------|

Reporting group description:

Lapatinib: Events up to 30 days post-treatment

| | |
|-----------------------|-------------|
| Reporting group title | Trastuzumab |
|-----------------------|-------------|

Reporting group description:

Trastuzumab: Events up to 30 days post-treatment

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Trastuzumab followed by Lapatinib |
|-----------------------|-----------------------------------|

Reporting group description:

Trastuzumab followed by Lapatinib: Events up to 30 days post-treatment

| Serious adverse events | Lapatinib plus Trastuzumab | Lapatinib | Trastuzumab |
|---|----------------------------|---------------------|---------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 379 / 2061 (18.39%) | 394 / 2056 (19.16%) | 251 / 2076 (12.09%) |
| number of deaths (all causes) | 6 | 12 | 3 |
| number of deaths resulting from adverse events | 2 | 3 | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ADENOCARCINOMA OF COLON | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ACUTE LYMPHOCYTIC LEUKAEMIA | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| ACUTE PROMYELOCYTIC LEUKAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 CARCINOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 STROMAL TUMOUR | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HAEMANGIOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BENIGN BREAST NEOPLASM | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BENIGN OVARIAN TUMOUR | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRIC CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (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 |
| BORDERLINE OVARIAN TUMOUR | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 3 / 2061 (0.15%) | 3 / 2056 (0.15%) | 4 / 2076 (0.19%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BREAST CANCER IN SITU | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| COLON CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENDOMETRIAL ADENOCARCINOMA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BLADDER NEOPLASM | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| INTRADUCTAL PAPILLOMA OF BREAST | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTRADUCTAL PROLIFERATIVE BREAST LESION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LEIOMYOMA | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LEIOMYOSARCOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MENINGIOMA BENIGN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| LIPOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MALIGNANT MELANOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| MELANOCYTIC NAEVUS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MENINGIOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| LENTIGO MALIGNA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| METASTASES TO CENTRAL NERVOUS SYSTEM | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| NEUROENDOCRINE TUMOUR | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 ADENOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 GERM CELL TERATOMA BENIGN | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| RECTAL CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PANCREATIC CARCINOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PAPILLARY THYROID CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PARATHYROID TUMOUR BENIGN | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PLASMA CELL MYELOMA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| OVARIAN NEOPLASM | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SMALL CELL LUNG CANCER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SQUAMOUS CELL CARCINOMA OF THE VULVA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SUPERFICIAL SPREADING MELANOMA STAGE UNSPECIFIED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THYROID CANCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TRANSITIONAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| UTERINE CANCER | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| UTERINE LEIOMYOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOTENSION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| JUGULAR VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTENSIVE CRISIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CIRCULATORY COLLAPSE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EMBOLISM VENOUS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| FLUSHING | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| VENOUS THROMBOSIS LIMB | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| VASCULAR INSUFFICIENCY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| THROMBOSIS | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUPERFICIAL VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SUBCLAVIAN VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RHEUMATOID VASCULITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ORTHOSTATIC HYPOTENSION | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |
| ADVERSE DRUG REACTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ASTHENIA | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 4 / 2056 (0.19%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHILLS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHRONIC FATIGUE SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| DEATH | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| GRANULOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FAT NECROSIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| FATIGUE | | | |
| subjects affected / exposed | 5 / 2061 (0.24%) | 7 / 2056 (0.34%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 5 / 5 | 6 / 7 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FEELING COLD | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEVICE RELATED THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| IMPAIRED HEALING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IMPLANT SITE THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| INFLAMMATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LIPOGRANULOMA | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MALAISE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIPHERAL SWELLING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NECROSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OEDEMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 11 / 2061 (0.53%) | 13 / 2056 (0.63%) | 5 / 2076 (0.24%) |
| occurrences causally related to treatment / all | 6 / 13 | 4 / 13 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUDDEN DEATH | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |
| SARCOIDOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAPHYLACTOID REACTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 4 / 2061 (0.19%) | 1 / 2056 (0.05%) | 4 / 2076 (0.19%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 1 | 3 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| BREAST HAEMATOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|------------------|------------------|
| ADENOMYOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 CALCIFICATIONS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BREAST DISORDER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| BREAST FIBROSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 INFLAMMATION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 NECROSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 SWELLING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ENDOMETRIAL HYPERPLASIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UTERINE POLYP | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OVARIAN CYST | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OVARIAN CYST RUPTURED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 PAIN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| POSTMENOPAUSAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| INTERMENSTRUAL BLEEDING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VAGINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 | | | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ATELECTASIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| BRONCHIECTASIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPHONIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| DYSPNOEA | | | |
| subjects affected / exposed | 4 / 2061 (0.19%) | 2 / 2056 (0.10%) | 6 / 2076 (0.29%) |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 2 | 2 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EPISTAXIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| COUGH | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOXIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARYNGEAL OEDEMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| LUNG CONSOLIDATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LUNG DISORDER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURISY | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLEURITIC PAIN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 5 / 2076 (0.24%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LUNG INFILTRATION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 6 / 2056 (0.29%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 6 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| PULMONARY GRANULOMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PULMONARY MASS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| PULMONARY THROMBOSIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Psychiatric disorders | | | |
| RESTLESSNESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SCHIZOPHRENIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABNORMAL BEHAVIOUR | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| MENTAL DISORDER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COMPLETED SUICIDE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 3 / 2061 (0.15%) | 1 / 2056 (0.05%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ALCOHOL WITHDRAWAL SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Product issues | | | |
| THROMBOSIS IN DEVICE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEVICE DISLOCATION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| DEVICE EXPULSION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Investigations | | | |
| BLOOD BILIRUBIN INCREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ALANINE AMINOTRANSFERASE | | | |

| | | | |
|---|------------------|------------------|------------------|
| INCREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| AMYLASE INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BLOOD MAGNESIUM DECREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BLOOD POTASSIUM DECREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BLOOD UREA INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BLOOD URINE PRESENT | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ELECTROCARDIOGRAM ST SEGMENT DEPRESSION | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| COAGULATION TEST ABNORMAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EJECTION FRACTION DECREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ELECTROCARDIOGRAM ABNORMAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ELECTROCARDIOGRAM QT PROLONGED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| BODY TEMPERATURE INCREASED | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ELECTROCARDIOGRAM T WAVE INVERSION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |

| | | | |
|---|------------------|------------------|------------------|
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTERNATIONAL NORMALISED RATIO INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LIPASE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LIVER FUNCTION TEST INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PLATELET COUNT DECREASED | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LIPASE INCREASED | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ALCOHOL POISONING | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARBON MONOXIDE POISONING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| FIBULA FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FOOT FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| 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 | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| FRACTURED COCCYX | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 INJURY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 SPRAIN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HIP FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MULTIPLE INJURIES | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIATION FIBROSIS - LUNG | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIATION PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| RIB FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SEROMA | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| STERNAL FRACTURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUBDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THERMAL BURN | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER LIMB FRACTURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WRIST FRACTURE | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (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 |
| WOUND COMPLICATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| Congenital, familial and genetic disorders | | | |
| GILBERT'S SYNDROME | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ATRIAL TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 5 / 2061 (0.24%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ANGINA PECTORIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 24 / 2061 (1.16%) | 7 / 2056 (0.34%) | 19 / 2076 (0.92%) |
| occurrences causally related to treatment / all | 24 / 24 | 4 / 7 | 19 / 19 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 1 / 1 |
| ACUTE CORONARY SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LEFT VENTRICULAR DYSFUNCTION | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 4 / 2056 (0.19%) | 4 / 2076 (0.19%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 4 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTRACARDIAC THROMBUS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| CARDIOMYOPATHY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| CARDIAC VENTRICULAR THROMBOSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERICARDITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERICARDIAL EFFUSION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PALPITATIONS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VENTRICULAR ARRHYTHMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| VENTRICULAR EXTRASYSTOLES | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| VENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Nervous system disorders | | | |
| AMYOTROPHIC LATERAL SCLEROSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| 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 HYPOXIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CEREBELLAR ATAXIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CEREBROVASCULAR ACCIDENT | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIZZINESS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EPILEPSY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 PARALYSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 2 / 2061 (0.10%) | 3 / 2056 (0.15%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOTONIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MIGRAINE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MOTOR NEURONE DISEASE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NEUROPATHY PERIPHERAL | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIPHERAL MOTOR NEUROPATHY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 ANEURYSM | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| POLYNEUROPATHY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| QUADRIPARESIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEIZURE | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEROTONIN SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SOMNOLENCE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNCOPE | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 2 / 2061 (0.10%) | 3 / 2056 (0.15%) | 5 / 2076 (0.24%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TRANSIENT GLOBAL AMNESIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SUBARACHNOID HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| 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 | | | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 20 / 2061 (0.97%) | 13 / 2056 (0.63%) | 7 / 2076 (0.34%) |
| occurrences causally related to treatment / all | 23 / 23 | 13 / 13 | 7 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 7 / 2076 (0.34%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 7 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 37 / 2061 (1.80%) | 36 / 2056 (1.75%) | 20 / 2076 (0.96%) |
| occurrences causally related to treatment / all | 49 / 49 | 37 / 37 | 24 / 24 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IRON DEFICIENCY ANAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAEMIA | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 7 / 2061 (0.34%) | 13 / 2056 (0.63%) | 7 / 2076 (0.34%) |
| occurrences causally related to treatment / all | 7 / 8 | 11 / 13 | 5 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EOSINOPHILIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 10 / 2061 (0.49%) | 12 / 2056 (0.58%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 9 / 10 | 12 / 13 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| AGRANULOCYTOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Ear and labyrinth disorders | | | |
| VERTIGO POSITIONAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| VERTIGO | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TINNITUS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Eye disorders | | | |
| DIPLOPIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| RETINAL DETACHMENT | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERIORBITAL OEDEMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAL FISSURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ANAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COLITIS | | | |
| subjects affected / exposed | 4 / 2061 (0.19%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL MASS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABDOMINAL DISTENSION | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |
| subjects affected / exposed | 6 / 2061 (0.29%) | 4 / 2056 (0.19%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 5 / 7 | 3 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRITIS EROSIVE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIARRHOEA | | | |
| subjects affected / exposed | 53 / 2061 (2.57%) | 44 / 2056 (2.14%) | 9 / 2076 (0.43%) |
| occurrences causally related to treatment / all | 56 / 58 | 46 / 48 | 6 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DUODENAL ULCER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| DYSPHAGIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ENTERITIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| EPIPLOIC APPENDAGITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRITIS | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL PERFORATION | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 TOXICITY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL ULCER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LOWER GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ILEUS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LARGE INTESTINE PERFORATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HAEMORRHOIDS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 4 / 2076 (0.19%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| NAUSEA | | | |
| subjects affected / exposed | 5 / 2061 (0.24%) | 7 / 2056 (0.34%) | 6 / 2076 (0.29%) |
| occurrences causally related to treatment / all | 4 / 5 | 6 / 7 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OESOPHAGITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PANCREATITIS ACUTE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| REFLUX GASTRITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| STOMATITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UPPER GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VOLVULUS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| VOMITING | | | |
| subjects affected / exposed | 9 / 2061 (0.44%) | 9 / 2056 (0.44%) | 8 / 2076 (0.39%) |
| occurrences causally related to treatment / all | 8 / 10 | 8 / 9 | 4 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | | | |
| BILE DUCT STENOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| BILIARY COLIC | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 2 / 2056 (0.10%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 4 / 2056 (0.19%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DRUG-INDUCED LIVER INJURY | | | |

| | | | |
|---|------------------|-------------------|------------------|
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GALLBLADDER OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HEPATIC FAILURE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 ACUTE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HEPATIC LESION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HEPATITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HEPATOTOXICITY | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 5 / 2056 (0.24%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERBILIRUBINAEMIA | | | |
| subjects affected / exposed | 5 / 2061 (0.24%) | 18 / 2056 (0.88%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 5 / 5 | 18 / 19 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTRANSAMINASAEMIA | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 74 / 2061 (3.59%) | 86 / 2056 (4.18%) | 11 / 2076 (0.53%) |
| occurrences causally related to treatment / all | 95 / 98 | 101 / 104 | 6 / 12 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| JAUNDICE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| Skin and subcutaneous tissue disorders | | | |
| ERYTHEMA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ACNE | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANGIODERMATITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANGIOEDEMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CUTANEOUS VASCULITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RASH | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 4 / 2061 (0.19%) | 7 / 2056 (0.34%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 7 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PRURITUS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKIN NECROSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| 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 SWELLING | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SKIN ULCER | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| PHOTOSENSITIVITY REACTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| NAIL DISORDER | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERTROPHIC SCAR | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| EXFOLIATIVE RASH | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| TOXIC EPIDERMAL NECROLYSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| URTICARIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| NEPHRITIC SYNDROME | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| NEPHROLITHIASIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 FAILURE | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| URINARY BLADDER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| URETHRAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| Endocrine disorders | | | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HYPERPARATHYROIDISM | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GOITRE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| AUTOIMMUNE THYROIDITIS | | | |

| | | | |
|--|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BACK PAIN | | | |
| subjects affected / exposed | 4 / 2061 (0.19%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| MYALGIA | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHEST WALL NECROSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COSTOCHONDRITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| LUMBAR SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| 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 CHEST PAIN | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| BONE PAIN | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MYOSITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| OSTEOPOROSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SCLERODERMA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SYNOVIAL CYST | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SYNOVITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SPONDYLOLISTHESIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| ABDOMINAL WALL ABSCESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ABSCESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ACUTE HEPATITIS B | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ACUTE SINUSITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| AMOEBIIC DYSENTERY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| BACTERIAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| ANTIBIOTIC ASSOCIATED COLITIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ANAL ABSCESS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BREAST CELLULITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| BRONCHITIS VIRAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| CATHETER SITE CELLULITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| CELLULITIS | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 15 / 2061 (0.73%) | 7 / 2056 (0.34%) | 5 / 2076 (0.24%) |
| occurrences causally related to treatment / all | 5 / 16 | 1 / 7 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 8 / 2061 (0.39%) | 4 / 2056 (0.19%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 1 / 8 | 1 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHLAMYDIAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CLOSTRIDIUM DIFFICILE INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| CYSTITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| CHEST WALL ABSCESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 INFECTIOUS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| DIVERTICULITIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ERYSIPPEL | | | |
| subjects affected / exposed | 6 / 2061 (0.29%) | 4 / 2056 (0.19%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTRIC INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 3 / 2056 (0.15%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROENTERITIS VIRAL | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| H1N1 INFLUENZA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HEPATITIS B | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HEPATITIS C | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| DEVICE RELATED SEPSIS | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HEPATITIS VIRAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| IMPLANT SITE CELLULITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INFECTED CYST | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INFECTED LYMPHOCELE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| LOCALISED INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| INFLUENZA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INTERVERTEBRAL DISCITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARGE INTESTINE INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LARYNGITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| INFECTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LYMPH GLAND INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LYMPH NODE ABSCESS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| LYMPHANGITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MALARIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MENINGITIS VIRAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| NAIL INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| NEUROBORRELIOSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| MASTITIS | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 2061 (0.10%) | 6 / 2056 (0.29%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OESOPHAGEAL CANDIDIASIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| OESOPHAGEAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| OSTEOMYELITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OTITIS MEDIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OVARIAN ABSCESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PERITONITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PHARYNGITIS | | | |

| | | | |
|---|-------------------|------------------|-------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PNEUMOCYSTIS JIROVECI INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 14 / 2061 (0.68%) | 9 / 2056 (0.44%) | 10 / 2076 (0.48%) |
| occurrences causally related to treatment / all | 8 / 14 | 2 / 9 | 4 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| PARONYCHIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 CYTOMEGALOVIRAL | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| POSTOPERATIVE WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 | 2 / 2061 (0.10%) | 0 / 2056 (0.00%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SKIN INFECTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 2 / 2056 (0.10%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 5 / 2056 (0.24%) | 5 / 2076 (0.24%) |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 5 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| SIALOADENITIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 2 / 2076 (0.10%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TUBERCULOUS PLEURISY | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| UPPER RESPIRATORY TRACT INFECTION | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| SOFT TISSUE INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STAPHYLOCOCCAL BACTERAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| STAPHYLOCOCCAL INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TUBERCULOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| STREPTOCOCCAL SEPSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| SUBCUTANEOUS ABSCESS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUPERINFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| TOOTH INFECTION | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STREPTOCOCCAL INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| UPPER RESPIRATORY TRACT INFECTION BACTERIAL | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 2061 (0.10%) | 2 / 2056 (0.10%) | 7 / 2076 (0.34%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | 1 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| UROSEPSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 INFECTION | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| WOUND INFECTION BACTERIAL | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |

| | | | |
|---|-------------------|-------------------|------------------|
| subjects affected / exposed | 11 / 2061 (0.53%) | 12 / 2056 (0.58%) | 4 / 2076 (0.19%) |
| occurrences causally related to treatment / all | 11 / 11 | 11 / 13 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 3 / 2061 (0.15%) | 3 / 2056 (0.15%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERCHOLESTEROLAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPERNATRAEMIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HYPERPHOSPHATASAEMIA | | | |
| subjects affected / exposed | 4 / 2061 (0.19%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOPHAGIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HYPOCALCAEMIA | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 2 / 2061 (0.10%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 8 / 2061 (0.39%) | 9 / 2056 (0.44%) | 3 / 2076 (0.14%) |
| occurrences causally related to treatment / all | 9 / 9 | 7 / 9 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 1 / 2056 (0.05%) | 0 / 2076 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 1 / 2056 (0.05%) | 0 / 2076 (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 |
| HYPERURICAEMIA | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 0 / 2076 (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 |
| HYPOVOLAEMIA | | | |
| subjects affected / exposed | 1 / 2061 (0.05%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| METABOLIC ACIDOSIS | | | |
| subjects affected / exposed | 0 / 2061 (0.00%) | 0 / 2056 (0.00%) | 1 / 2076 (0.05%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------|-----------------------------------|--|--|
| Serious adverse events | Trastuzumab followed by Lapatinib | | |
|-------------------------------|-----------------------------------|--|--|

| | | | |
|---|------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 299 / 2076 (14.40%) | | |
| number of deaths (all causes) | 5 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ADENOCARCINOMA OF COLON | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ACUTE LYMPHOCYTIC LEUKAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ACUTE PROMYELOCYTIC LEUKAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROINTESTINAL CARCINOMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROINTESTINAL STROMAL TUMOUR | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HAEMANGIOMA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BENIGN BREAST NEOPLASM | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| BENIGN OVARIAN TUMOUR | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTRIC CANCER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BORDERLINE OVARIAN TUMOUR | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BREAST CANCER | | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| BREAST CANCER IN SITU | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COLON CANCER | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ENDOMETRIAL ADENOCARCINOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLADDER NEOPLASM | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTRADUCTAL PAPILLOMA OF BREAST | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTRADUCTAL PROLIFERATIVE BREAST LESION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LEIOMYOMA | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LEIOMYOSARCOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MENINGIOMA BENIGN | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LIPOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MALIGNANT MELANOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MELANOCYTIC NAEVUS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MENINGIOMA | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LENTIGO MALIGNA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| METASTASES TO CENTRAL NERVOUS SYSTEM | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| NEUROENDOCRINE TUMOUR | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| OVARIAN ADENOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| OVARIAN CANCER | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| OVARIAN GERM CELL TERATOMA BENIGN | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| RECTAL CANCER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PANCREATIC CARCINOMA | | | | |

| | | | | |
|--|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PAPILLARY THYROID CANCER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PARATHYROID TUMOUR BENIGN | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PLASMA CELL MYELOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| OVARIAN NEOPLASM | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| SMALL CELL LUNG CANCER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SQUAMOUS CELL CARCINOMA OF THE VULVA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SUPERFICIAL SPREADING MELANOMA STAGE UNSPECIFIED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| THYROID CANCER | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TRANSITIONAL CELL CARCINOMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UTERINE CANCER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UTERINE LEIOMYOMA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOTENSION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| JUGULAR VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERTENSIVE CRISIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CIRCULATORY COLLAPSE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EMBOLISM VENOUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FLUSHING | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VENOUS THROMBOSIS LIMB | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VASCULAR INSUFFICIENCY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| THROMBOSIS | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUPERFICIAL VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUBCLAVIAN VEIN THROMBOSIS | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RHEUMATOID VASCULITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ORTHOSTATIC HYPOTENSION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| ADVERSE DRUG REACTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ASTHENIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHEST PAIN | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHILLS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHRONIC FATIGUE SYNDROME | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEATH | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GRANULOMA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FAT NECROSIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FATIGUE | | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FEELING COLD | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| DEVICE RELATED THROMBOSIS | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| IMPAIRED HEALING | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| IMPLANT SITE THROMBOSIS | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INFLAMMATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LIPOGRANULOMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MALAISE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERIPHERAL SWELLING | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NECROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NON-CARDIAC CHEST PAIN | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OEDEMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OEDEMA PERIPHERAL | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PYREXIA | | | |
| subjects affected / exposed | 16 / 2076 (0.77%) | | |
| occurrences causally related to treatment / all | 8 / 17 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUDDEN DEATH | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Immune system disorders | | | |
| SARCOIDOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAPHYLACTIC REACTION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAPHYLACTOID REACTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERSENSITIVITY | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| BREAST HAEMATOMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ADENOMYOSIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST CALCIFICATIONS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST DISORDER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST FIBROSIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST INFLAMMATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST NECROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST SWELLING | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENDOMETRIAL HYPERPLASIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UTERINE POLYP | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OVARIAN CYST | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OVARIAN CYST RUPTURED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PELVIC PAIN | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| POSTMENOPAUSAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INTERMENSTRUAL BLEEDING | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VAGINAL HAEMORRHAGE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| ACUTE RESPIRATORY DISTRESS SYNDROME | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATELECTASIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHIECTASIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HAEMOPTYSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSPHONIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSPNOEA | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSPNOEA EXERTIONAL | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COUGH | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOXIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LARYNGEAL OEDEMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LUNG CONSOLIDATION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LUNG DISORDER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMOTHORAX | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PLEURISY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PLEURITIC PAIN | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONITIS | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LUNG INFILTRATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PULMONARY GRANULOMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PULMONARY MASS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PULMONARY THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| RESTLESSNESS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SCHIZOPHRENIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABNORMAL BEHAVIOUR | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MENTAL DISORDER | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COMPLETED SUICIDE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| DEPRESSION | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| INSOMNIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MAJOR DEPRESSION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ALCOHOL WITHDRAWAL SYNDROME | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| THROMBOSIS IN DEVICE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEVICE DISLOCATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEVICE EXPULSION | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| BLOOD BILIRUBIN INCREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| AMYLASE INCREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLOOD ALKALINE PHOSPHATASE INCREASED | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLOOD MAGNESIUM DECREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLOOD POTASSIUM DECREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BLOOD UREA INCREASED | | | |

| | | | | |
|--|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| BLOOD URINE PRESENT | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ELECTROCARDIOGRAM ST SEGMENT DEPRESSION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COAGULATION TEST ABNORMAL | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| EJECTION FRACTION DECREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ELECTROCARDIOGRAM ABNORMAL | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ELECTROCARDIOGRAM QT PROLONGED | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | | |
|---|------------------|--|--|--|
| BODY TEMPERATURE INCREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ELECTROCARDIOGRAM T WAVE INVERSION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTERNATIONAL NORMALISED RATIO INCREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LIPASE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LIVER FUNCTION TEST INCREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PLATELET COUNT DECREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| WEIGHT DECREASED | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|------------------|--|--|
| LIPASE INCREASED | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ALCOHOL POISONING | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CARBON MONOXIDE POISONING | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| CONCUSSION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FIBULA FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FOOT FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| FOREIGN BODY | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FRACTURE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| FRACTURED COCCYX | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOWER LIMB FRACTURE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HUMERUS FRACTURE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFUSION RELATED REACTION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LIGAMENT INJURY | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LIGAMENT SPRAIN | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| HIP FRACTURE | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MULTIPLE INJURIES | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PELVIC FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIATION FIBROSIS - LUNG | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIATION PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RADIUS FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RIB FRACTURE | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ROAD TRAFFIC ACCIDENT | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEROMA | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SPINAL FRACTURE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| STERNAL FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUBDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| THERMAL BURN | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TIBIA FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UPPER LIMB FRACTURE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| WRIST FRACTURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| WOUND COMPLICATION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| GILBERT'S SYNDROME | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| ATRIOVENTRICULAR BLOCK COMPLETE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATRIAL THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| ATRIAL TACHYCARDIA | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ATRIAL FIBRILLATION | | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ARRHYTHMIA | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ANGINA PECTORIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ACUTE MYOCARDIAL INFARCTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| CARDIAC FAILURE CONGESTIVE | | | | |
| subjects affected / exposed | 6 / 2076 (0.29%) | | | |
| occurrences causally related to treatment / all | 6 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ACUTE CORONARY SYNDROME | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| MYOCARDIAL INFARCTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LEFT VENTRICULAR DYSFUNCTION | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 5 / 2076 (0.24%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INTRACARDIAC THROMBUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CARDIOMYOPATHY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CARDIAC VENTRICULAR THROMBOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUPRAVENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERICARDITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERICARDIAL EFFUSION | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PALPITATIONS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VENTRICULAR ARRHYTHMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VENTRICULAR EXTRASYSTOLES | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VENTRICULAR TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| AMYOTROPHIC LATERAL SCLEROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRAIN HYPOXIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| CEREBELLAR ATAXIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CEREBROVASCULAR ACCIDENT | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EPILEPSY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FACIAL PARALYSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEADACHE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOTONIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MIGRAINE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MOTOR NEURONE DISEASE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERIPHERAL MOTOR NEUROPATHY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INTRACRANIAL ANEURYSM | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| POLYNEUROPATHY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| QUADRIPARESIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEIZURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEROTONIN SYNDROME | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SOMNOLENCE | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TRANSIENT GLOBAL AMNESIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SUBARACHNOID HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 21 / 2076 (1.01%) | | |
| occurrences causally related to treatment / all | 25 / 25 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| IRON DEFICIENCY ANAEMIA | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAEMIA | | | |
| subjects affected / exposed | 6 / 2076 (0.29%) | | |
| occurrences causally related to treatment / all | 7 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EOSINOPHILIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 6 / 2076 (0.29%) | | |
| occurrences causally related to treatment / all | 6 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| AGRANULOCYTOSIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| VERTIGO POSITIONAL | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VERTIGO | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TINNITUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|------------------|--|--|
| DIPLOPIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RETINAL DETACHMENT | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERIORBITAL OEDEMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN LOWER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAL FISSURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COLITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABDOMINAL MASS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTRITIS EROSIIVE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 6 / 2076 (0.29%) | | |
| occurrences causally related to treatment / all | 5 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DUODENAL ULCER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DYSPHAGIA | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENTERITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EPIPLOIC APPENDAGITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTRIC ULCER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTRITIS | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROINTESTINAL OBSTRUCTION | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROINTESTINAL PERFORATION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROINTESTINAL TOXICITY | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| GASTROINTESTINAL ULCER | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOWER GASTROINTESTINAL HAEMORRHAGE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| ILEUS | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTESTINAL HAEMORRHAGE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTESTINAL OBSTRUCTION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LARGE INTESTINE PERFORATION | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NAUSEA | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OESOPHAGITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCREATITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PANCREATITIS ACUTE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| REFLUX GASTRITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| STOMATITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UPPER GASTROINTESTINAL HAEMORRHAGE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VOLVULUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VOMITING | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| BILE DUCT STENOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BILIARY COLIC | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOLELITHIASIS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DRUG-INDUCED LIVER INJURY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GALLBLADDER OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATIC FAILURE | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHOLECYSTITIS ACUTE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATIC LESION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATOTOXICITY | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERBILIRUBINAEMIA | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 12 / 2076 (0.58%) | | |
| occurrences causally related to treatment / all | 12 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERTRANSAMINASAEMIA | | | |
| subjects affected / exposed | 55 / 2076 (2.65%) | | |
| occurrences causally related to treatment / all | 67 / 74 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| JAUNDICE | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| ERYTHEMA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ACNE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANGIODERMATITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANGIOEDEMA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CUTANEOUS VASCULITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DERMATITIS ACNEIFORM | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RASH | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PRURITUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKIN NECROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKIN SWELLING | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKIN ULCER | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PHOTOSENSITIVITY REACTION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NAIL DISORDER | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERTROPHIC SCAR | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| EXFOLIATIVE RASH | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TOXIC EPIDERMAL NECROLYSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URTICARIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| ACUTE KIDNEY INJURY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CALCULUS URINARY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEPHRITIC SYNDROME | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RENAL COLIC | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URINARY BLADDER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URETHRAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| HYPOTHYROIDISM | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERPARATHYROIDISM | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GOITRE | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| AUTOIMMUNE THYROIDITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MYALGIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHEST WALL NECROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COSTOCHONDRITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LUMBAR SPINAL STENOSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MUSCULOSKELETAL CHEST PAIN | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BONE PAIN | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MYOSITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOPOROSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SCLERODERMA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SYNOVIAL CYST | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SYNOVITIS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SPONDYLOLISTHESIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| ABDOMINAL WALL ABSCESS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ABSCESS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ACUTE HEPATITIS B | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ACUTE SINUSITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| AMOEBIC DYSENTERY | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BACTERIAL INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAL INFECTION | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANTIBIOTIC ASSOCIATED COLITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BACTERAEemia | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ANAL ABSCESS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BREAST CELLULITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHITIS | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| BRONCHITIS VIRAL | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CATHETER SITE CELLULITIS | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CELLULITIS | | | |
| subjects affected / exposed | 14 / 2076 (0.67%) | | |
| occurrences causally related to treatment / all | 10 / 17 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHLAMYDIAL INFECTION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CLOSTRIDIUM DIFFICILE INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CYSTITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CHEST WALL ABSCESS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIARRHOEA INFECTIOUS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIVERTICULITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ERYSIPELAS | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTRIC INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROENTERITIS VIRAL | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GASTROINTESTINAL INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| H1N1 INFLUENZA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATITIS B | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATITIS C | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DEVICE RELATED SEPSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HEPATITIS VIRAL | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HERPES ZOSTER | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| IMPLANT SITE CELLULITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INFECTED CYST | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INFECTED LYMPHOCELE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LOCALISED INFECTION | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFLUENZA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INTERVERTEBRAL DISCITIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LARGE INTESTINE INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LARYNGITIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| INFECTION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LOWER RESPIRATORY TRACT INFECTION | | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| LYMPH GLAND INFECTION | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LYMPH NODE ABSCESS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| LYMPHANGITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MALARIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MENINGITIS VIRAL | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NAIL INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| NEUROBORRELIOSIS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| MASTITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OESOPHAGEAL CANDIDIASIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OESOPHAGEAL INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OSTEOMYELITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OTITIS MEDIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OVARIAN ABSCESS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PNEUMONIA ASPIRATION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PERITONITIS | | | |

| | | | | |
|---|-------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PHARYNGITIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PNEUMOCYSTIS JIROVECI INFECTION | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PNEUMONIA | | | | |
| subjects affected / exposed | 11 / 2076 (0.53%) | | | |
| occurrences causally related to treatment / all | 2 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PARONYCHIA | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PNEUMONIA CYTOMEGALOVIRAL | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| POST PROCEDURAL INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| POSTOPERATIVE WOUND INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SKIN INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SEPSIS | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SIALOADENITIS | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| SINUSITIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PYELONEPHRITIS ACUTE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TUBERCULOUS PLEURISY | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SOFT TISSUE INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| STAPHYLOCOCCAL BACTERAEMIA | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| STAPHYLOCOCCAL INFECTION | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| TUBERCULOSIS | | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| STREPTOCOCCAL SEPSIS | | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SUBCUTANEOUS ABSCESS | | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| SUPERINFECTION | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| TOOTH INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| STREPTOCOCCAL INFECTION | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UPPER RESPIRATORY TRACT INFECTION BACTERIAL | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 6 / 2076 (0.29%) | | |
| occurrences causally related to treatment / all | 4 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| UROSEPSIS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| WOUND INFECTION | | | |
| subjects affected / exposed | 2 / 2076 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| WOUND INFECTION BACTERIAL | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 3 / 2076 (0.14%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| DIABETES MELLITUS | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERCHOLESTEROLAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERNATRAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERPHOSPHATASAEMIA | | | |
| subjects affected / exposed | 4 / 2076 (0.19%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOPHAGIA | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOCALCAEMIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 1 / 2076 (0.05%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOMAGNESAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPERURICAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOPHOSPHATAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| HYPOVOLAEMIA | | | |
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| METABOLIC ACIDOSIS | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 0 / 2076 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Lapatinib plus Trastuzumab | Lapatinib | Trastuzumab |
|---|----------------------------|----------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1930 / 2061 (93.64%) | 1887 / 2056 (91.78%) | 1649 / 2076 (79.43%) |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 211 / 2061 (10.24%) | 190 / 2056 (9.24%) | 272 / 2076 (13.10%) |
| occurrences (all) | 232 | 199 | 294 |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 227 / 2061 (11.01%) | 132 / 2056 (6.42%) | 171 / 2076 (8.24%) |
| occurrences (all) | 270 | 158 | 208 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 144 / 2061 (6.99%) | 138 / 2056 (6.71%) | 160 / 2076 (7.71%) |
| occurrences (all) | 158 | 153 | 184 |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 227 / 2061 (11.01%) | 164 / 2056 (7.98%) | 114 / 2076 (5.49%) |
| occurrences (all) | 265 | 193 | 126 |
| FATIGUE | | | |
| subjects affected / exposed | 511 / 2061 (24.79%) | 443 / 2056 (21.55%) | 439 / 2076 (21.15%) |
| occurrences (all) | 603 | 502 | 550 |
| ASTHENIA | | | |
| subjects affected / exposed | 202 / 2061 (9.80%) | 175 / 2056 (8.51%) | 171 / 2076 (8.24%) |
| occurrences (all) | 259 | 208 | 213 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 219 / 2061 (10.63%) | 153 / 2056 (7.44%) | 242 / 2076 (11.66%) |
| occurrences (all) | 252 | 173 | 282 |
| DYSPNOEA | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed | 147 / 2061 (7.13%) | 103 / 2056 (5.01%) | 170 / 2076 (8.19%) |
| occurrences (all) | 151 | 106 | 202 |
| EPISTAXIS | | | |
| subjects affected / exposed | 319 / 2061 (15.48%) | 244 / 2056 (11.87%) | 165 / 2076 (7.95%) |
| occurrences (all) | 363 | 268 | 179 |
| Psychiatric disorders | | | |
| INSOMNIA | | | |
| subjects affected / exposed | 168 / 2061 (8.15%) | 152 / 2056 (7.39%) | 190 / 2076 (9.15%) |
| occurrences (all) | 182 | 163 | 220 |
| Injury, poisoning and procedural complications | | | |
| RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 91 / 2061 (4.42%) | 82 / 2056 (3.99%) | 129 / 2076 (6.21%) |
| occurrences (all) | 92 | 82 | 132 |
| Cardiac disorders | | | |
| LEFT VENTRICULAR DYSFUNCTION | | | |
| subjects affected / exposed | 59 / 2061 (2.86%) | 45 / 2056 (2.19%) | 107 / 2076 (5.15%) |
| occurrences (all) | 65 | 49 | 115 |
| Nervous system disorders | | | |
| DIRZINESS | | | |
| subjects affected / exposed | 104 / 2061 (5.05%) | 115 / 2056 (5.59%) | 118 / 2076 (5.68%) |
| occurrences (all) | 111 | 122 | 130 |
| HEADACHE | | | |
| subjects affected / exposed | 192 / 2061 (9.32%) | 161 / 2056 (7.83%) | 262 / 2076 (12.62%) |
| occurrences (all) | 227 | 193 | 314 |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 177 / 2061 (8.59%) | 173 / 2056 (8.41%) | 178 / 2076 (8.57%) |
| occurrences (all) | 189 | 185 | 197 |
| PARAESTHESIA | | | |
| subjects affected / exposed | 125 / 2061 (6.07%) | 107 / 2056 (5.20%) | 131 / 2076 (6.31%) |
| occurrences (all) | 141 | 114 | 181 |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 164 / 2061 (7.96%) | 162 / 2056 (7.88%) | 194 / 2076 (9.34%) |
| occurrences (all) | 201 | 175 | 232 |
| Blood and lymphatic system disorders | | | |
| LEUKOPENIA | | | |

| | | | |
|-----------------------------|----------------------|----------------------|---------------------|
| subjects affected / exposed | 174 / 2061 (8.44%) | 155 / 2056 (7.54%) | 168 / 2076 (8.09%) |
| occurrences (all) | 300 | 268 | 295 |
| ANAEMIA | | | |
| subjects affected / exposed | 226 / 2061 (10.97%) | 169 / 2056 (8.22%) | 223 / 2076 (10.74%) |
| occurrences (all) | 255 | 184 | 253 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 233 / 2061 (11.31%) | 220 / 2056 (10.70%) | 179 / 2076 (8.62%) |
| occurrences (all) | 396 | 365 | 292 |
| Gastrointestinal disorders | | | |
| STOMATITIS | | | |
| subjects affected / exposed | 203 / 2061 (9.85%) | 161 / 2056 (7.83%) | 98 / 2076 (4.72%) |
| occurrences (all) | 249 | 185 | 114 |
| NAUSEA | | | |
| subjects affected / exposed | 393 / 2061 (19.07%) | 381 / 2056 (18.53%) | 285 / 2076 (13.73%) |
| occurrences (all) | 504 | 471 | 387 |
| DYSPEPSIA | | | |
| subjects affected / exposed | 174 / 2061 (8.44%) | 156 / 2056 (7.59%) | 116 / 2076 (5.59%) |
| occurrences (all) | 181 | 173 | 124 |
| CONSTIPATION | | | |
| subjects affected / exposed | 120 / 2061 (5.82%) | 135 / 2056 (6.57%) | 156 / 2076 (7.51%) |
| occurrences (all) | 132 | 143 | 194 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 137 / 2061 (6.65%) | 110 / 2056 (5.35%) | 78 / 2076 (3.76%) |
| occurrences (all) | 160 | 119 | 86 |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 146 / 2061 (7.08%) | 148 / 2056 (7.20%) | 79 / 2076 (3.81%) |
| occurrences (all) | 164 | 164 | 101 |
| DIARRHOEA | | | |
| subjects affected / exposed | 1516 / 2061 (73.56%) | 1278 / 2056 (62.16%) | 399 / 2076 (19.22%) |
| occurrences (all) | 2752 | 1973 | 527 |
| VOMITING | | | |
| subjects affected / exposed | 251 / 2061 (12.18%) | 215 / 2056 (10.46%) | 151 / 2076 (7.27%) |
| occurrences (all) | 334 | 278 | 180 |
| Hepatobiliary disorders | | | |

| | | | |
|--|--------------------------------|-------------------------------|-------------------------------|
| HYPERTRANSAMINASAEMIA subjects affected / exposed occurrences (all) | 348 / 2061 (16.89%) 600 | 366 / 2056 (17.80%) 657 | 281 / 2076 (13.54%) 482 |
| HYPERBILIRUBINAEMIA subjects affected / exposed occurrences (all) | 96 / 2061 (4.66%) 133 | 121 / 2056 (5.89%) 165 | 31 / 2076 (1.49%) 39 |
| Skin and subcutaneous tissue disorders PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME subjects affected / exposed occurrences (all) | 181 / 2061 (8.78%) 197 | 126 / 2056 (6.13%) 130 | 47 / 2076 (2.26%) 50 |
| PRURITUS subjects affected / exposed occurrences (all) | 316 / 2061 (15.33%) 380 | 334 / 2056 (16.25%) 382 | 134 / 2076 (6.45%) 145 |
| ACNE subjects affected / exposed occurrences (all) | 134 / 2061 (6.50%) 149 | 112 / 2056 (5.45%) 123 | 20 / 2076 (0.96%) 21 |
| ALOPECIA subjects affected / exposed occurrences (all) | 109 / 2061 (5.29%) 109 | 110 / 2056 (5.35%) 111 | 151 / 2076 (7.27%) 152 |
| DERMATITIS ACNEIFORM subjects affected / exposed occurrences (all) | 117 / 2061 (5.68%) 138 | 124 / 2056 (6.03%) 146 | 19 / 2076 (0.92%) 24 |
| DRY SKIN subjects affected / exposed occurrences (all) | 262 / 2061 (12.71%) 282 | 280 / 2056 (13.62%) 305 | 86 / 2076 (4.14%) 92 |
| ERYTHEMA subjects affected / exposed occurrences (all) | 122 / 2061 (5.92%) 149 | 93 / 2056 (4.52%) 112 | 87 / 2076 (4.19%) 99 |
| NAIL DISORDER subjects affected / exposed occurrences (all) | 359 / 2061 (17.42%) 384 | 294 / 2056 (14.30%) 312 | 220 / 2076 (10.60%) 231 |
| RASH subjects affected / exposed occurrences (all) | 771 / 2061 (37.41%) 1010 | 767 / 2056 (37.31%) 959 | 223 / 2076 (10.74%) 265 |
| SKIN FISSURES | | | |

| | | | |
|--|---------------------------|---------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 145 / 2061 (7.04%) 165 | 123 / 2056 (5.98%) 139 | 7 / 2076 (0.34%) 8 |
| Musculoskeletal and connective tissue disorders | | | |
| MYALGIA | | | |
| subjects affected / exposed | 211 / 2061 (10.24%) | 174 / 2056 (8.46%) | 252 / 2076 (12.14%) |
| occurrences (all) | 274 | 231 | 368 |
| BONE PAIN | | | |
| subjects affected / exposed | 87 / 2061 (4.22%) | 91 / 2056 (4.43%) | 122 / 2076 (5.88%) |
| occurrences (all) | 103 | 107 | 146 |
| BACK PAIN | | | |
| subjects affected / exposed | 128 / 2061 (6.21%) | 119 / 2056 (5.79%) | 126 / 2076 (6.07%) |
| occurrences (all) | 138 | 124 | 133 |
| ARTHRALGIA | | | |
| subjects affected / exposed | 340 / 2061 (16.50%) | 320 / 2056 (15.56%) | 451 / 2076 (21.72%) |
| occurrences (all) | 404 | 366 | 559 |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 135 / 2061 (6.55%) | 98 / 2056 (4.77%) | 175 / 2076 (8.43%) |
| occurrences (all) | 154 | 109 | 216 |
| Infections and infestations | | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 117 / 2061 (5.68%) | 93 / 2056 (4.52%) | 118 / 2076 (5.68%) |
| occurrences (all) | 144 | 107 | 149 |
| PARONYCHIA | | | |
| subjects affected / exposed | 262 / 2061 (12.71%) | 206 / 2056 (10.02%) | 22 / 2076 (1.06%) |
| occurrences (all) | 323 | 247 | 26 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 128 / 2061 (6.21%) | 96 / 2056 (4.67%) | 150 / 2076 (7.23%) |
| occurrences (all) | 152 | 108 | 189 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 223 / 2061 (10.82%) | 188 / 2056 (9.14%) | 142 / 2076 (6.84%) |
| occurrences (all) | 268 | 215 | 173 |
| HYPERPHOSPHATASAEMIA | | | |

| | | | |
|-----------------------------|-------------------|--------------------|-------------------|
| subjects affected / exposed | 81 / 2061 (3.93%) | 120 / 2056 (5.84%) | 76 / 2076 (3.66%) |
| occurrences (all) | 95 | 127 | 87 |

| | | | |
|---|-----------------------------------|--|--|
| Non-serious adverse events | Trastuzumab followed by Lapatinib | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1862 / 2076 (89.69%) | | |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 225 / 2076 (10.84%) | | |
| occurrences (all) | 240 | | |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 188 / 2076 (9.06%) | | |
| occurrences (all) | 222 | | |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 149 / 2076 (7.18%) | | |
| occurrences (all) | 174 | | |
| MUCOSAL INFLAMMATION | | | |
| subjects affected / exposed | 149 / 2076 (7.18%) | | |
| occurrences (all) | 171 | | |
| FATIGUE | | | |
| subjects affected / exposed | 515 / 2076 (24.81%) | | |
| occurrences (all) | 615 | | |
| ASTHENIA | | | |
| subjects affected / exposed | 178 / 2076 (8.57%) | | |
| occurrences (all) | 218 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 201 / 2076 (9.68%) | | |
| occurrences (all) | 225 | | |
| DYSPNOEA | | | |
| subjects affected / exposed | 146 / 2076 (7.03%) | | |
| occurrences (all) | 155 | | |
| EPISTAXIS | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed | 213 / 2076 (10.26%) | | |
| occurrences (all) | 238 | | |
| Psychiatric disorders INSOMNIA | | | |
| subjects affected / exposed | 172 / 2076 (8.29%) | | |
| occurrences (all) | 187 | | |
| Injury, poisoning and procedural complications RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 127 / 2076 (6.12%) | | |
| occurrences (all) | 129 | | |
| Cardiac disorders LEFT VENTRICULAR DYSFUNCTION | | | |
| subjects affected / exposed | 46 / 2076 (2.22%) | | |
| occurrences (all) | 52 | | |
| Nervous system disorders DIZZINESS | | | |
| subjects affected / exposed | 127 / 2076 (6.12%) | | |
| occurrences (all) | 138 | | |
| HEADACHE | | | |
| subjects affected / exposed | 241 / 2076 (11.61%) | | |
| occurrences (all) | 295 | | |
| NEUROPATHY PERIPHERAL | | | |
| subjects affected / exposed | 183 / 2076 (8.82%) | | |
| occurrences (all) | 192 | | |
| PARAESTHESIA | | | |
| subjects affected / exposed | 110 / 2076 (5.30%) | | |
| occurrences (all) | 131 | | |
| PERIPHERAL SENSORY NEUROPATHY | | | |
| subjects affected / exposed | 159 / 2076 (7.66%) | | |
| occurrences (all) | 177 | | |
| Blood and lymphatic system disorders LEUKOPENIA | | | |
| subjects affected / exposed | 138 / 2076 (6.65%) | | |
| occurrences (all) | 225 | | |
| ANAEMIA | | | |

| | | | |
|-----------------------------|----------------------|--|--|
| subjects affected / exposed | 168 / 2076 (8.09%) | | |
| occurrences (all) | 186 | | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 175 / 2076 (8.43%) | | |
| occurrences (all) | 303 | | |
| Gastrointestinal disorders | | | |
| STOMATITIS | | | |
| subjects affected / exposed | 141 / 2076 (6.79%) | | |
| occurrences (all) | 159 | | |
| NAUSEA | | | |
| subjects affected / exposed | 393 / 2076 (18.93%) | | |
| occurrences (all) | 496 | | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 140 / 2076 (6.74%) | | |
| occurrences (all) | 151 | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 184 / 2076 (8.86%) | | |
| occurrences (all) | 211 | | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 111 / 2076 (5.35%) | | |
| occurrences (all) | 121 | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 108 / 2076 (5.20%) | | |
| occurrences (all) | 120 | | |
| DIARRHOEA | | | |
| subjects affected / exposed | 1039 / 2076 (50.05%) | | |
| occurrences (all) | 1450 | | |
| VOMITING | | | |
| subjects affected / exposed | 181 / 2076 (8.72%) | | |
| occurrences (all) | 220 | | |
| Hepatobiliary disorders | | | |
| HYPERTRANSAMINASAEMIA | | | |
| subjects affected / exposed | 378 / 2076 (18.21%) | | |
| occurrences (all) | 637 | | |
| HYPERBILIRUBINAEMIA | | | |

| | | | |
|---|------------------------|--|--|
| subjects affected / exposed | 103 / 2076 (4.96%) | | |
| occurrences (all) | 133 | | |
| Skin and subcutaneous tissue disorders | | | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 105 / 2076 (5.06%) | | |
| occurrences (all) | 111 | | |
| PRURITUS | | | |
| subjects affected / exposed | 268 / 2076 (12.91%) | | |
| occurrences (all) | 304 | | |
| ACNE | | | |
| subjects affected / exposed | 138 / 2076 (6.65%) | | |
| occurrences (all) | 144 | | |
| ALOPECIA | | | |
| subjects affected / exposed | 135 / 2076 (6.50%) | | |
| occurrences (all) | 137 | | |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed | 96 / 2076 (4.62%) | | |
| occurrences (all) | 106 | | |
| DRY SKIN | | | |
| subjects affected / exposed | 244 / 2076 (11.75%) | | |
| occurrences (all) | 265 | | |
| ERYTHEMA | | | |
| subjects affected / exposed | 104 / 2076 (5.01%) | | |
| occurrences (all) | 116 | | |
| NAIL DISORDER | | | |
| subjects affected / exposed | 272 / 2076 (13.10%) | | |
| occurrences (all) | 285 | | |
| RASH | | | |
| subjects affected / exposed | 685 / 2076 (33.00%) | | |
| occurrences (all) | 862 | | |
| SKIN FISSURES | | | |
| subjects affected / exposed | 98 / 2076 (4.72%) | | |
| occurrences (all) | 103 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-------------------------------|--|--|
| MYALGIA subjects affected / exposed occurrences (all) | 214 / 2076 (10.31%) 289 | | |
| BONE PAIN subjects affected / exposed occurrences (all) | 109 / 2076 (5.25%) 130 | | |
| BACK PAIN subjects affected / exposed occurrences (all) | 133 / 2076 (6.41%) 140 | | |
| ARTHRALGIA subjects affected / exposed occurrences (all) | 348 / 2076 (16.76%) 415 | | |
| PAIN IN EXTREMITY subjects affected / exposed occurrences (all) | 125 / 2076 (6.02%) 140 | | |
| Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) | 96 / 2076 (4.62%) 113 | | |
| PARONYCHIA subjects affected / exposed occurrences (all) | 165 / 2076 (7.95%) 185 | | |
| NASOPHARYNGITIS subjects affected / exposed occurrences (all) | 111 / 2076 (5.35%) 128 | | |
| Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all) | 173 / 2076 (8.33%) 189 | | |
| HYPERPHOSPHATASAEMIA subjects affected / exposed occurrences (all) | 109 / 2076 (5.25%) 118 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 April 2008 | Amendment No. 01: Implementation of additional monitoring of liver enzymes and associated criteria for study drug discontinuation, modification of the study inclusion/ exclusion criteria, provide clarification to the length of follow up, and permitted chemotherapy regimens. To provide clarification regarding the dosing of study therapy and the management of AEs. |
| 14 August 2008 | Amendment No. 02: Implementation of a lower starting dose of lapatinib (750 mg) during chemotherapy only in the Lap+Tras arm of Design 2 to diminish the chance of diarrhea occurrence. To allow patients randomized in the Tras-Lap arm of both designs to receive lapatinib after the occurrence of a secondary cardiac endpoint during trastuzumab administration only if LVEF after the washout period (6 weeks) and prior to lapatinib administration is $\geq 50\%$. To clarify the extent and nature of future translational research studies and provide revised timelines for circulating tumor cell collection. |
| 12 February 2009 | Amendment No. 03: Inclusion of statement indicating the possible accrual imbalance between Design 1 and Design 2 and possible future need to close screening to a design. |
| 19 March 2009 | Amendment No. 04: To allow the inclusion of docetaxel in Design 2, implement an additional interim analysis for analyses at 400, 700 and 1000 DFS events with final analysis after 1388 DFS events, and allow the use of Breast MRI scans instead of mammograms. |
| 20 November 2009 | Amendment No. 05: Inclusion of Design 2B and associated updates to enrollment (maximum sample size of 8400 patients) and revised timelines for circulating tumor cell collection. |
| 27 January 2010 | Amendment No. 06: Reduction of lapatinib dose when used concurrently with chemotherapy in the Lap arm and the Lap+Tras arm of Designs 2 and 2B to diminish the chance of diarrhea occurrence. |
| 29 March 2010 | Amendment No. 07: To clarify statistical plans for interim and final analyses, include the collection of a FFPE tumor block for future research, to update additional medicines added to the prohibited medications list for patients taking lapatinib. |
| 02 August 2010 | Amendment No. 08: To add a new statistical section entitled "Registration Strategy for ALTTO – June 2010", and thus support the modification of the analysis plan by the sponsor at the time (GSK). Inclusion of a statement clarifying that after completion of study treatment, patients enrolled in this study may receive anti-cancer therapy in other trials only if the trial has been approved by the Steering Committee. Clarification regarding the reporting of post-study treatment long-term AEs, Grade 4 neutropenia/leukopenia as an SAE, diarrhea management in lapatinib-containing arms, and the dose adjustments of trastuzumab and chemotherapy due to substantial weight changes and overweight/obese patients. Inclusion of the collection of a FNA sample will be allowed for certain patients. |
| 28 October 2010 | Amendment No. 09: Add NCI/CTEP recommendation for the calculation of the carboplatin dose and to add the maximum dose of carboplatin based on the target area under the curve (AUC) 6 is 900 mg. |

| | |
|-----------------|--|
| 17 October 2011 | Amendment No. 10: To implement the recommendations by the ALTTO Steering Committee due to the IDMC meeting (August 18, 2011). Guidance for patient withdrawal from the study while allowing for collection of OS information, patients who were considered lost to follow-up, regarding prohibited medications and future trial medications. Clarification of diarrhea management, assessments beyond study treatment completion to determine secondary cardiac event, lobular carcinoma in situ and ductal carcinoma in situ reporting. |
| 18 March 2016 | Amendment No. 11: To update the assessment schedule, specify that after the patient completed the 10-year follow-up post randomization, only drug-related SAEs were to be reported, add the definition of EOS for clarity purposes, add details regarding explorative subgroup analyses of DFS for specific risk factors, allow broader use of the previously collected pharmacogenetic samples and the previously generated genetic data, and to implement changes in secondary endpoints. |
| 05 July 2016 | Amendment No. 12: To delete or replace references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship, and to make administrative changes to align with study-specific processes and procedures. As the burden on patients was reduced by decreasing the number of procedures that required a physical visit to the site, the optional collection of samples at the time of relapse was also deleted. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com> for complete trial results.

Notes: