

**Clinical trial results:****A Randomized, Open-Label, Phase 3 Study of Abemaciclib Combined with Standard Adjuvant Endocrine Therapy versus Standard Adjuvant Endocrine Therapy Alone in Patients with High Risk, Node Positive, Early Stage, Hormone Receptor Positive, Human Epidermal Receptor 2 Negative, Breast Cancer****Summary**

| | |
|--------------------------|---|
| EudraCT number | 2016-004362-26 |
| Trial protocol | DE NL HU GB BE DK FI PL GR AT ES CZ FR PT IT RO |
| Global end of trial date | |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 31 March 2021 |
| First version publication date | 31 March 2021 |

Trial information**Trial identification**

| | |
|-----------------------|-------------|
| Sponsor protocol code | I3Y-MC-JPCF |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|---------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03155997 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 16338 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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 | Interim |
| Date of interim/final analysis | 16 March 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 March 2020 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and efficacy of the study drug abemaciclib in participants with high risk, node positive, early stage, hormone receptor positive (HR+), human epidermal receptor 2 negative (HER2-), breast cancer.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 12 July 2017 |
| 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: 145 |
| Country: Number of subjects enrolled | Australia: 217 |
| Country: Number of subjects enrolled | Austria: 42 |
| Country: Number of subjects enrolled | Belgium: 116 |
| Country: Number of subjects enrolled | Brazil: 297 |
| Country: Number of subjects enrolled | Canada: 44 |
| Country: Number of subjects enrolled | China: 357 |
| Country: Number of subjects enrolled | Czechia: 27 |
| Country: Number of subjects enrolled | Denmark: 112 |
| Country: Number of subjects enrolled | Finland: 94 |
| Country: Number of subjects enrolled | France: 187 |
| Country: Number of subjects enrolled | Germany: 300 |
| Country: Number of subjects enrolled | Greece: 138 |
| Country: Number of subjects enrolled | Hong Kong: 20 |
| Country: Number of subjects enrolled | Hungary: 52 |
| Country: Number of subjects enrolled | India: 112 |
| Country: Number of subjects enrolled | Israel: 77 |
| Country: Number of subjects enrolled | Italy: 131 |
| Country: Number of subjects enrolled | Japan: 377 |
| Country: Number of subjects enrolled | Mexico: 225 |
| Country: Number of subjects enrolled | Netherlands: 19 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | New Zealand: 43 |
| Country: Number of subjects enrolled | Poland: 125 |
| Country: Number of subjects enrolled | Portugal: 37 |
| Country: Number of subjects enrolled | Puerto Rico: 4 |
| Country: Number of subjects enrolled | Romania: 113 |
| Country: Number of subjects enrolled | Russian Federation: 139 |
| Country: Number of subjects enrolled | Saudi Arabia: 14 |
| Country: Number of subjects enrolled | Singapore: 32 |
| Country: Number of subjects enrolled | South Africa: 9 |
| Country: Number of subjects enrolled | Korea, Republic of: 245 |
| Country: Number of subjects enrolled | Spain: 292 |
| Country: Number of subjects enrolled | Sweden: 12 |
| Country: Number of subjects enrolled | Taiwan: 124 |
| Country: Number of subjects enrolled | Turkey: 235 |
| Country: Number of subjects enrolled | Ukraine: 105 |
| Country: Number of subjects enrolled | United Kingdom: 199 |
| Country: Number of subjects enrolled | United States: 820 |
| Worldwide total number of subjects | 5637 |
| EEA total number of subjects | 1797 |

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) | 4787 |
| From 65 to 84 years | 850 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Completers included participants who had recurrence disease, death due to any cause, and participants off treatment but on study follow-up.

Pre-assignment

Screening details:

No Text Available

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 | 150 mg Abemaciclib + Endocrine Therapy |

Arm description:

Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Abemaciclib |
| Investigational medicinal product code | |
| Other name | LY2835219 |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first.

| | |
|--|---|
| Investigational medicinal product name | Standard Adjuvant Endocrine Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection, Oral liquid, Tablet |
| Routes of administration | Intramuscular use, Oral use, Subcutaneous use |

Dosage and administration details:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| | |
|------------------|-------------------|
| Arm title | Endocrine Therapy |
|------------------|-------------------|

Arm description:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Standard Adjuvant Endocrine Therapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection, Oral liquid, Tablet |
| Routes of administration | Intramuscular use, Oral use, Subcutaneous use |

Dosage and administration details:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| Number of subjects in period 1 | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy |
|--|---|--------------------------|
| Started | 2808 | 2829 |
| Received at least one dose of study drug | 2791 | 2800 |
| Completed | 650 | 607 |
| Not completed | 2158 | 2222 |
| Missing disposition data | - | 1 |
| Consent withdrawn by subject | 119 | 134 |
| On study treatment | 2027 | 2074 |
| Lost to follow-up | 12 | 13 |

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | 150 mg Abemaciclib + Endocrine Therapy |
| Reporting group description: | |
| Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met. | |
| Reporting group title | Endocrine Therapy |
| Reporting group description: | |
| Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met. | |

| Reporting group values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | Total |
|--|--|-------------------|-------|
| Number of subjects | 2808 | 2829 | 5637 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 52.20 | 52.10 | |
| standard deviation | ± 11.26 | ± 11.20 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 2787 | 2814 | 5601 |
| Male | 21 | 15 | 36 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 355 | 378 | 733 |
| Not Hispanic or Latino | 1734 | 1738 | 3472 |
| Unknown or Not Reported | 719 | 713 | 1432 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 64 | 58 | 122 |
| Asian | 675 | 669 | 1344 |
| Native Hawaiian or Other Pacific Islander | 3 | 4 | 7 |
| Black or African American | 57 | 53 | 110 |
| White | 1947 | 1978 | 3925 |
| More than one race | 22 | 25 | 47 |

| Unknown or Not Reported | 40 | 42 | 82 |
|-------------------------|-----|-----|-----|
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Argentina | 77 | 68 | 145 |
| Australia | 108 | 109 | 217 |
| Austria | 22 | 20 | 42 |
| Belgium | 65 | 51 | 116 |
| Brazil | 144 | 153 | 297 |
| Canada | 28 | 16 | 44 |
| China | 187 | 170 | 357 |
| Czechia | 15 | 12 | 27 |
| Denmark | 54 | 58 | 112 |
| Finland | 45 | 49 | 94 |
| France | 86 | 101 | 187 |
| Germany | 148 | 152 | 300 |
| Greece | 74 | 64 | 138 |
| Hong Kong | 8 | 12 | 20 |
| Hungary | 24 | 28 | 52 |
| India | 59 | 53 | 112 |
| Israel | 39 | 38 | 77 |
| Italy | 72 | 59 | 131 |
| Japan | 181 | 196 | 377 |
| Mexico | 104 | 121 | 225 |
| Netherlands | 5 | 14 | 19 |
| New Zealand | 21 | 22 | 43 |
| Poland | 65 | 60 | 125 |
| Portugal | 21 | 16 | 37 |
| Puerto Rico | 1 | 3 | 4 |
| Romania | 53 | 60 | 113 |
| Russia | 66 | 73 | 139 |
| Saudi Arabia | 5 | 9 | 14 |
| Singapore | 11 | 21 | 32 |
| South Africa | 3 | 6 | 9 |
| South Korea | 122 | 123 | 245 |
| Spain | 144 | 148 | 292 |
| Sweden | 7 | 5 | 12 |
| Taiwan | 64 | 60 | 124 |
| Turkey | 125 | 110 | 235 |
| Ukraine | 54 | 51 | 105 |
| United Kingdom | 99 | 100 | 199 |
| United States | 402 | 418 | 820 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | 150 mg Abemaciclib + Endocrine Therapy |
| Reporting group description: Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met. | |
| Reporting group title | Endocrine Therapy |
| Reporting group description: Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met. | |

Primary: Invasive Disease Free Survival (IDFS)

| | |
|---|---------------------------------------|
| End point title | Invasive Disease Free Survival (IDFS) |
| End point description: IDFS, as defined by the STEEP System, was measured from the date of randomization to the date of first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive cancer, death attributable to any cause. Analysis Population Description: All randomized participants (including the censored participants). 2672 participants were censored in "150 mg Abemaciclib + Endocrine Therapy," 2642 participants were censored in "Endocrine Therapy." | |
| End point type | Primary |
| End point timeframe: Baseline to Recurrence or Death from Any Cause (Up to 32 Months) | |

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|----------------------------------|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2808 ^[1] | 2829 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | | |

Notes:

[1] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

[2] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Invasive Disease Free Survival (IDFS) |
| Comparison groups | 150 mg Abemaciclib + Endocrine Therapy v Endocrine Therapy |

| | |
|---|-------------------|
| Number of subjects included in analysis | 5637 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00957 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.747 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.598 |
| upper limit | 0.932 |

Secondary: IDFS for Participants with Ki-67 Index $\geq 20\%$

| | |
|---|--|
| End point title | IDFS for Participants with Ki-67 Index $\geq 20\%$ |
| End point description: | |
| Outcome data will be provided after the study is completed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Recurrence or Death from Any Cause (Approximately 10 Years) | |

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|----------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[3] - Outcome data will be provided after the study is completed.

[4] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Relapse-Free Survival (DRFS)

| | |
|--|--------------------------------------|
| End point title | Distant Relapse-Free Survival (DRFS) |
| End point description: | |
| Distant relapse-free survival is defined as the time from randomization to distant recurrence or death from any cause, whichever occurs first. | |
| Analysis Population Description: All randomized participants (including the censored participants). 2702 participants were censored in "150 mg Abemaciclib + Endocrine Therapy," 2677 participants were censored in "Endocrine Therapy." | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Distant Recurrence or Death from Any Cause (Up to 32 Months) | |

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|----------------------------------|--|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2808 ^[5] | 2829 ^[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 9999 (9999 to 9999) | | |

Notes:

[5] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

[6] - 9999 = NA, There were not enough events to compute a median or 95% confidence interval.

Statistical analyses

| Statistical analysis title | Distant Relapse-Free Survival (DRFS) |
|---|--|
| Comparison groups | 150 mg Abemaciclib + Endocrine Therapy v Endocrine Therapy |
| Number of subjects included in analysis | 5637 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.717 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.559 |
| upper limit | 0.92 |

Secondary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| Outcome data will be provided after the study is completed. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Death from Any Cause (Approximately 10 Years) | |

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|----------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[7] - Outcome data will be provided after the study is completed.

[8] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Minimum Steady State Concentration (C_{min,ss}) of Abemaciclib

| | |
|-----------------|--|
| End point title | Pharmacokinetics (PK): Minimum Steady State Concentration (C _{min,ss}) of Abemaciclib ^[9] |
|-----------------|--|

End point description:

Pharmacokinetics (PK): Minimum Steady State Concentration (C_{min,ss}) of Abemaciclib

Analysis Population Description: All randomized participants who received at least one dose of Abemaciclib and had evaluable PK data.

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

End point timeframe:

Day 1 (2 hours post-dose), Days 30, 60, 90 post-dose

Notes:

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

Justification: No inferential statistics were planned for this endpoint.

| | | | | |
|---|--|--|--|--|
| End point values | 150 mg Abemaciclib + Endocrine Therapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 483 | | | |
| Units: Nanograms per milliliter (ng/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 143 (± 110) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Cancer Therapy - Breast (FACT-B)

| | |
|-----------------|---|
| End point title | Change from Baseline on the Functional Assessment of Cancer Therapy - Breast (FACT-B) |
|-----------------|---|

End point description:

Outcome data will be provided after the study is completed.

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

End point timeframe:

Baseline, Follow Up (Approximately 3 Years)

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|-------------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[10] - Outcome data will be provided after the study is completed.

[11] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES)

| | |
|-----------------|--|
| End point title | Change from Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES) |
|-----------------|--|

End point description:

Outcome data will be provided after the study is completed.

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

End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|-------------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[12] - Outcome data will be provided after the study is completed.

[13] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)

| | |
|-----------------|--|
| End point title | Change from Baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) |
|-----------------|--|

End point description:

Outcome data will be provided after the study is completed.

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

End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|-------------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[14] - Outcome data will be provided after the study is completed.

[15] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L)

| | |
|-----------------|--|
| End point title | Change from Baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L) |
|-----------------|--|

End point description:

Outcome data will be provided after the study is completed.

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

End point timeframe:

Baseline, Follow Up (Approximately 3 Years)]

| End point values | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | | |
|-------------------------------------|--|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | () | () | | |

Notes:

[16] - Outcome data will be provided after the study is completed.

[17] - Outcome data will be provided after the study is completed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up To 32 Months

Adverse event reporting additional description:

I3Y-MC-JPCF

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | 150 mg Abemaciclib + Endocrine Therapy |
|-----------------------|--|

Reporting group description:

Participants received Abemaciclib orally at 150 milligrams (mg) twice daily with at least 6 hours between doses for up to 2 years or until evidence of disease recurrence or other discontinuation criteria were met, whichever occurs first. Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| | |
|-----------------------|-------------------|
| Reporting group title | Endocrine Therapy |
|-----------------------|-------------------|

Reporting group description:

Endocrine therapy (physicians' choice) standard-of-care was administered according to package label until discontinuation criteria were met.

| Serious adverse events | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | |
|---|--|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 344 / 2791 (12.33%) | 202 / 2800 (7.21%) | |
| number of deaths (all causes) | 38 | 36 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| acute lymphocytic leukaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cervix carcinoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[1] | 0 / 2770 (0.00%) | 2 / 2785 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colon cancer | | | |

| | | | |
|--|------------------|------------------|--|
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colorectal carcinoma stage 0 | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| endometrial neoplasm | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[2] | 0 / 2770 (0.00%) | 1 / 2785 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fibroadenoma of breast | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal adenocarcinoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| malignant melanoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| meningioma benign | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| non-small cell lung cancer | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| papillary thyroid cancer | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thyroid adenoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thyroid cancer | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tumour pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| uterine leiomyoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[3] | 1 / 2770 (0.04%) | 2 / 2785 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-------------------|------------------|--|
| Vascular disorders | | | |
| deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 16 / 2791 (0.57%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 12 / 17 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| embolism | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haematoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypertension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| jugular vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphoedema | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 5 / 2791 (0.18%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| peripheral artery thrombosis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombophlebitis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombophlebitis superficial alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| capsular contracture associated with breast implant alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chest pain alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fatigue alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| general physical health deterioration alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| hyperplasia alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| impaired healing alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| inflammation alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| non-cardiac chest pain alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pain alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|------------------------------------|------------------------------------|--|
| pyrexia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 7 / 2791 (0.25%) 4 / 7 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| sudden death alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| Immune system disorders anaphylactic reaction alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| drug hypersensitivity alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| Reproductive system and breast disorders adenomyosis alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[4] occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2770 (0.04%) 1 / 1 0 / 0 | 0 / 2785 (0.00%) 0 / 0 0 / 0 | |
| breast atrophy alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 2 0 / 0 | |
| breast calcifications | | | |

| | | | |
|--|------------------|------------------|--|
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast discharge | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast fibrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast inflammation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast mass | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast necrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast swelling | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cervical dysplasia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[5] | 2 / 2770 (0.07%) | 0 / 2785 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| endometrial disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[6] | 0 / 2770 (0.00%) | 1 / 2785 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| endometrial hypertrophy | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[7] | 0 / 2770 (0.00%) | 2 / 2785 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| endometrial thickening | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed ^[8] | 1 / 2770 (0.04%) | 1 / 2785 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|--|
| <p>endometriosis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[9]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | <p>1 / 2785 (0.04%)</p> <p>1 / 1</p> <p>0 / 0</p> | |
| <p>fibrocystic breast disease</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 2791 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | <p>2 / 2800 (0.07%)</p> <p>0 / 2</p> <p>0 / 0</p> | |
| <p>metrorrhagia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[10]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | <p>1 / 2785 (0.04%)</p> <p>0 / 1</p> <p>0 / 0</p> | |
| <p>ovarian cyst</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[11]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>0 / 2770 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | <p>3 / 2785 (0.11%)</p> <p>0 / 3</p> <p>0 / 0</p> | |
| <p>pelvic haematoma</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>1 / 2791 (0.04%)</p> <p>0 / 1</p> <p>0 / 0</p> | <p>0 / 2800 (0.00%)</p> <p>0 / 0</p> <p>0 / 0</p> | |
| <p>uterine polyp</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[12]</p> <p>occurrences causally related to treatment / all</p> <p>deaths causally related to treatment / all</p> | <p>2 / 2770 (0.07%)</p> <p>0 / 2</p> <p>0 / 0</p> | <p>3 / 2785 (0.11%)</p> <p>1 / 3</p> <p>0 / 0</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>asthma</p> <p>alternative dictionary used: MedDRA 23.0</p> | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chronic obstructive pulmonary disease | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoxia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| interstitial lung disease | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| organising pneumonia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pleural effusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia aspiration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 7 / 2791 (0.25%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 16 / 2791 (0.57%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 14 / 16 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| respiratory failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| bipolar disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| confusional state | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| delirium | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| depression | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mania | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mental disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| psychotic disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| suicide attempt | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|------------------|------------------|--|
| Product issues | | | |
| device failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| alanine aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 2791 (0.18%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| aspartate aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 2791 (0.18%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| blood creatinine increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| international normalised ratio increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| occult blood | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| transaminases increased | | | |

| | | | |
|--|------------------|------------------|--|
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| abdominal wound dehiscence | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| alcohol poisoning | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast procedural complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| clavicle fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| exposure during pregnancy | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fall | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| femoral neck fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| foot fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hip fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|--|------------------|------------------|--|
| incisional hernia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| jaw fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| joint injury | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ligament rupture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| post procedural haematoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| post procedural haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| postoperative adhesion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| postoperative thoracic procedure complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| postoperative wound complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| procedural complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| radiation pneumonitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| radius fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rib fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin flap necrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| spinal fracture | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thermal burn | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound dehiscence | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 4 / 2800 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound necrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| wrist fracture alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| Cardiac disorders acute left ventricular failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| angina pectoris alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 1 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| atrial fibrillation alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 6 / 2791 (0.21%) 2 / 6 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| atrioventricular block complete alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| cardiac arrest alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 2791 (0.07%) 1 / 2 0 / 1 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| cardiac failure alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 2791 (0.14%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| cardiotoxicity | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| coronary artery disease | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myocardial infarction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| myocardial ischaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pericarditis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sinus tachycardia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| stress cardiomyopathy alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| supraventricular tachycardia alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ventricular fibrillation alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| carotid artery aneurysm alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| carpal tunnel syndrome alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebral haemorrhage alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| cerebral infarction alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebral ischaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebral venous thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebrospinal fluid leakage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebrovascular accident | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| dizziness | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| extrapyramidal disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| headache | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hemiparesis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ischaemic stroke | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| memory impairment | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| monoparesis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| movement disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nerve compression | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neuropathy | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| presyncope | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subarachnoid haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| syncope | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| transient ischaemic attack | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| trigeminal neuralgia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 8 / 2791 (0.29%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 4 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bone marrow oedema | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| disseminated intravascular coagulation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| febrile neutropenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| leukopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphadenopathy mediastinal | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 3 / 2791 (0.11%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pancytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombocytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 2791 (0.14%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| tympanic membrane perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vertigo | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| angle closure glaucoma | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cataract | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| eyelid ptosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| macular hole | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| macular pseudohole | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| retinal detachment | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| abdominal pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 6 / 2791 (0.21%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal fissure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| anal fistula | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| chronic gastritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colitis ischaemic | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dental caries | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 15 / 2791 (0.54%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 13 / 18 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

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|--|------------------|------------------|--|
| enteritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| food poisoning | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastritis erosive | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal fistula | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhoidal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhoids | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| inguinal hernia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intestinal obstruction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| large intestine polyp | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nausea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oesophagitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| pancreatitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 6 / 2791 (0.21%) 1 / 6 0 / 0 | 2 / 2800 (0.07%) 0 / 2 0 / 0 | |
| pancreatitis acute alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 2791 (0.07%) 1 / 2 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| peritoneal adhesions alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| stomatitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 2791 (0.07%) 1 / 2 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| umbilical hernia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| vomiting alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 2791 (0.11%) 2 / 3 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| Hepatobiliary disorders biliary colic alternative dictionary used: MedDRA 23.0 | | | |

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|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholecystitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 10 / 2791 (0.36%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholecystitis acute | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholelithiasis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| drug-induced liver injury | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic cirrhosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic function abnormal | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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| jaundice alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| Skin and subcutaneous tissue disorders erythema alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| Renal and urinary disorders acute kidney injury alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 4 / 2791 (0.14%) 3 / 4 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| nephrolithiasis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 2791 (0.11%) 0 / 3 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| renal failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 2791 (0.07%) 1 / 2 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| renal impairment alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 1 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| tubulointerstitial nephritis alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| back pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fistula | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| flank pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intervertebral disc protrusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| myositis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neck pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteoarthritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteonecrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rheumatoid arthritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rotator cuff syndrome | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| spinal osteoarthritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tenosynovitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|------------------------------------|------------------------------------|--|
| Infections and infestations abdominal infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 2791 (0.00%) 0 / 0 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| abscess alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 1 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| anal abscess alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| appendicitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 2791 (0.11%) 0 / 3 0 / 0 | 2 / 2800 (0.07%) 0 / 2 0 / 0 | |
| appendicitis perforated alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 2791 (0.04%) 0 / 1 0 / 0 | 0 / 2800 (0.00%) 0 / 0 0 / 0 | |
| bacteraemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 2791 (0.07%) 1 / 2 0 / 0 | 1 / 2800 (0.04%) 0 / 1 0 / 0 | |
| biliary tract infection alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|-------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast abscess | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| breast cellulitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 2791 (0.18%) | 4 / 2800 (0.14%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| campylobacter gastroenteritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cellulitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 11 / 2791 (0.39%) | 9 / 2800 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 13 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cellulitis staphylococcal | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|------------------|------------------|--|--|
| clostridium colitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| clostridium difficile colitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| coronavirus infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| device related infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 0 / 2791 (0.00%) | 2 / 2800 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| diverticulitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 3 / 2791 (0.11%) | 5 / 2800 (0.18%) | | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| ear infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| erysipelas alternative dictionary used: MedDRA 23.0 | | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 5 / 2791 (0.18%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| escherichia pyelonephritis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| febrile infection alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis clostridial alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatitis e alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| implant site infection alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|--|------------------|------------------|--|
| infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infective pulmonary exacerbation of cystic fibrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| influenza | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 7 / 2791 (0.25%) | 3 / 2800 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| intervertebral discitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| laryngitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lymphangitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mastitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 2791 (0.11%) | 5 / 2800 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mastoiditis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| meningitis viral | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutropenic infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteomyelitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-------------------|-------------------|--|
| peritonitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 23 / 2791 (0.82%) | 14 / 2800 (0.50%) | |
| occurrences causally related to treatment / all | 10 / 23 | 2 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| pneumonia bacterial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia influenzal | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia streptococcal | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| post procedural cellulitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| post procedural infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| postoperative wound infection alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyelonephritis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| respiratory tract infection alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 2791 (0.18%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| septic shock alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| skin infection alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-------------------|------------------|--|
| soft tissue infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tuberculosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 6 / 2791 (0.21%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 12 / 2791 (0.43%) | 4 / 2800 (0.14%) | |
| occurrences causally related to treatment / all | 1 / 12 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urosepsis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| viral infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| wound infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 2791 (0.07%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| dehydration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 7 / 2791 (0.25%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| food intolerance | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypercalcaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyperglycaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypocalcaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypokalaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 2791 (0.14%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyponatraemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 2 / 2800 (0.07%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypophosphataemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypovolaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 2791 (0.00%) | 1 / 2800 (0.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| metabolic acidosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 2791 (0.04%) | 0 / 2800 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | 150 mg Abemaciclib + Endocrine Therapy | Endocrine Therapy | |
|---|---|--------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2723 / 2791 (97.56%) | 2318 / 2800 (82.79%) | |
| Vascular disorders | | | |
| hot flush | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 393 / 2791 (14.08%) | 587 / 2800 (20.96%) | |
| occurrences (all) | 432 | 678 | |
| hypertension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 101 / 2791 (3.62%) | 130 / 2800 (4.64%) | |
| occurrences (all) | 120 | 158 | |
| hypotension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 33 / 2791 (1.18%) | 14 / 2800 (0.50%) | |
| occurrences (all) | 33 | 15 | |
| lymphoedema | | | |

| | | | |
|---|--|--|--|
| alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 282 / 2791 (10.10%) 295 | 207 / 2800 (7.39%) 225 | |
| Surgical and medical procedures breast reconstruction alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 28 / 2791 (1.00%) 28 | 22 / 2800 (0.79%) 25 | |
| General disorders and administration site conditions axillary pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) chest pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) chills alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) fatigue alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 28 / 2791 (1.00%) 28 35 / 2791 (1.25%) 40 49 / 2791 (1.76%) 55 1073 / 2791 (38.45%) 1434 | 39 / 2800 (1.39%) 41 35 / 2800 (1.25%) 36 18 / 2800 (0.64%) 18 433 / 2800 (15.46%) 522 | |
| influenza like illness alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) malaise alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) mucosal inflammation | 141 / 2791 (5.05%) 180 88 / 2791 (3.15%) 109 | 112 / 2800 (4.00%) 152 29 / 2800 (1.04%) 29 | |

| | | | |
|--|--------------------------------------|--------------------------------------|--|
| <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>72 / 2791 (2.58%)</p> <p>90</p> | <p>21 / 2800 (0.75%)</p> <p>32</p> | |
| <p>oedema peripheral</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>169 / 2791 (6.06%)</p> <p>200</p> | <p>103 / 2800 (3.68%)</p> <p>119</p> | |
| <p>pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>60 / 2791 (2.15%)</p> <p>64</p> | <p>53 / 2800 (1.89%)</p> <p>58</p> | |
| <p>peripheral swelling</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>51 / 2791 (1.83%)</p> <p>58</p> | <p>53 / 2800 (1.89%)</p> <p>61</p> | |
| <p>pyrexia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>227 / 2791 (8.13%)</p> <p>299</p> | <p>114 / 2800 (4.07%)</p> <p>130</p> | |
| <p>Reproductive system and breast disorders</p> <p>breast pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>95 / 2791 (3.40%)</p> <p>104</p> | <p>120 / 2800 (4.29%)</p> <p>133</p> | |
| <p>erectile dysfunction</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[13]</p> <p>occurrences (all)</p> | <p>1 / 21 (4.76%)</p> <p>1</p> | <p>0 / 15 (0.00%)</p> <p>0</p> | |
| <p>vaginal discharge</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed^[14]</p> <p>occurrences (all)</p> | <p>26 / 2770 (0.94%)</p> <p>27</p> | <p>39 / 2785 (1.40%)</p> <p>42</p> | |
| <p>vulvovaginal dryness</p> <p>alternative dictionary used: MedDRA 23.0</p> | | | |

| | | | |
|---|----------------------------|---------------------------|--|
| subjects affected / exposed ^[15] occurrences (all) | 78 / 2770 (2.82%) 80 | 117 / 2785 (4.20%) 127 | |
| Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 337 / 2791 (12.07%) 407 | 193 / 2800 (6.89%) 228 | |
| dyspnoea alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 139 / 2791 (4.98%) 154 | 77 / 2800 (2.75%) 86 | |
| epistaxis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 49 / 2791 (1.76%) 52 | 8 / 2800 (0.29%) 10 | |
| nasal congestion alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 34 / 2791 (1.22%) 37 | 29 / 2800 (1.04%) 33 | |
| oropharyngeal pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 115 / 2791 (4.12%) 142 | 76 / 2800 (2.71%) 91 | |
| pneumonitis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 36 / 2791 (1.29%) 36 | 10 / 2800 (0.36%) 10 | |
| productive cough alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 45 / 2791 (1.61%) 53 | 25 / 2800 (0.89%) 28 | |
| rhinitis allergic alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>rhinorrhoea</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>40 / 2791 (1.43%)</p> <p>41</p> <p>29 / 2791 (1.04%)</p> <p>31</p> | <p>40 / 2800 (1.43%)</p> <p>42</p> <p>15 / 2800 (0.54%)</p> <p>16</p> | |
| <p>Psychiatric disorders</p> <p>anxiety</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>depression</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>insomnia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>81 / 2791 (2.90%)</p> <p>84</p> <p>134 / 2791 (4.80%)</p> <p>142</p> <p>208 / 2791 (7.45%)</p> <p>251</p> | <p>113 / 2800 (4.04%)</p> <p>116</p> <p>116 / 2800 (4.14%)</p> <p>120</p> <p>218 / 2800 (7.79%)</p> <p>246</p> | |
| <p>Investigations</p> <p>alanine aminotransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>aspartate aminotransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>blood alkaline phosphatase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>blood creatinine increased</p> <p>alternative dictionary used: MedDRA 23.0</p> | <p>265 / 2791 (9.49%)</p> <p>345</p> <p>257 / 2791 (9.21%)</p> <p>323</p> <p>83 / 2791 (2.97%)</p> <p>98</p> | <p>119 / 2800 (4.25%)</p> <p>149</p> <p>106 / 2800 (3.79%)</p> <p>122</p> <p>47 / 2800 (1.68%)</p> <p>56</p> | |

| | | | |
|--|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>gamma-glutamyltransferase increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>weight decreased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>weight increased</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>277 / 2791 (9.92%)</p> <p>396</p> <p>70 / 2791 (2.51%)</p> <p>80</p> <p>79 / 2791 (2.83%)</p> <p>88</p> <p>29 / 2791 (1.04%)</p> <p>32</p> | <p>17 / 2800 (0.61%)</p> <p>22</p> <p>24 / 2800 (0.86%)</p> <p>28</p> <p>19 / 2800 (0.68%)</p> <p>20</p> <p>46 / 2800 (1.64%)</p> <p>47</p> | |
| <p>Injury, poisoning and procedural complications</p> <p>contusion</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>fall</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>procedural pain</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>42 / 2791 (1.50%)</p> <p>51</p> <p>52 / 2791 (1.86%)</p> <p>61</p> <p>73 / 2791 (2.62%)</p> <p>78</p> | <p>37 / 2800 (1.32%)</p> <p>38</p> <p>36 / 2800 (1.29%)</p> <p>43</p> <p>53 / 2800 (1.89%)</p> <p>64</p> | |
| <p>Cardiac disorders</p> <p>palpitations</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>54 / 2791 (1.93%)</p> <p>62</p> | <p>20 / 2800 (0.71%)</p> <p>22</p> | |
| Nervous system disorders | | | |

| | | | |
|--|---------------------------------|-------------------------------|--|
| dizziness alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 274 / 2791 (9.82%) 333 | 158 / 2800 (5.64%) 188 | |
| dysgeusia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 103 / 2791 (3.69%) 121 | 8 / 2800 (0.29%) 8 | |
| headache alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 482 / 2791 (17.27%) 809 | 359 / 2800 (12.82%) 553 | |
| memory impairment alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 29 / 2791 (1.04%) 32 | 22 / 2800 (0.79%) 22 | |
| neuropathy alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 193 / 2791 (6.92%) 221 | 203 / 2800 (7.25%) 234 | |
| taste disorder alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 36 / 2791 (1.29%) 36 | 4 / 2800 (0.14%) 4 | |
| Blood and lymphatic system disorders | | | |
| anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 634 / 2791 (22.72%) 862 | 88 / 2800 (3.14%) 113 | |
| leukopenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 1026 / 2791 (36.76%) 1706 | 171 / 2800 (6.11%) 244 | |
| lymphopenia | | | |

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|--|---|---|--|
| alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 372 / 2791 (13.33%) 527 | 94 / 2800 (3.36%) 118 | |
| neutropenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 1246 / 2791 (44.64%) 2316 | 140 / 2800 (5.00%) 214 | |
| thrombocytopenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 341 / 2791 (12.22%) 528 | 39 / 2800 (1.39%) 48 | |
| Ear and labyrinth disorders vertigo alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 70 / 2791 (2.51%) 93 | 47 / 2800 (1.68%) 55 | |
| Eye disorders dry eye alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) lacrimation increased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) vision blurred alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 71 / 2791 (2.54%) 76 137 / 2791 (4.91%) 158 46 / 2791 (1.65%) 52 | 28 / 2800 (1.00%) 31 10 / 2800 (0.36%) 10 24 / 2800 (0.86%) 25 | |
| Gastrointestinal disorders abdominal distension alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) abdominal pain | 75 / 2791 (2.69%) 90 | 27 / 2800 (0.96%) 28 | |

| | | | |
|---|----------------------------------|---------------------------|--|
| alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 945 / 2791 (33.86%) 1974 | 226 / 2800 (8.07%) 275 | |
| constipation alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 288 / 2791 (10.32%) 377 | 142 / 2800 (5.07%) 161 | |
| diarrhoea alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 2294 / 2791 (82.19%) 11663 | 199 / 2800 (7.11%) 288 | |
| dry mouth alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 94 / 2791 (3.37%) 103 | 25 / 2800 (0.89%) 27 | |
| dyspepsia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 205 / 2791 (7.35%) 264 | 61 / 2800 (2.18%) 66 | |
| flatulence alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 84 / 2791 (3.01%) 95 | 11 / 2800 (0.39%) 12 | |
| gastritis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 58 / 2791 (2.08%) 65 | 31 / 2800 (1.11%) 34 | |
| gastrooesophageal reflux disease alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 74 / 2791 (2.65%) 76 | 45 / 2800 (1.61%) 47 | |
| haemorrhoids alternative dictionary used: MedDRA 23.0 | | | |

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|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>mouth ulceration</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>nausea</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>68 / 2791 (2.44%)</p> <p>82</p> <p>39 / 2791 (1.40%)</p> <p>48</p> <p>779 / 2791 (27.91%)</p> <p>1203</p> | <p>28 / 2800 (1.00%)</p> <p>28</p> <p>3 / 2800 (0.11%)</p> <p>3</p> <p>222 / 2800 (7.93%)</p> <p>274</p> | |
| <p>stomatitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>toothache</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>vomiting</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>154 / 2791 (5.52%)</p> <p>212</p> <p>49 / 2791 (1.76%)</p> <p>55</p> <p>454 / 2791 (16.27%)</p> <p>744</p> | <p>30 / 2800 (1.07%)</p> <p>39</p> <p>42 / 2800 (1.50%)</p> <p>50</p> <p>117 / 2800 (4.18%)</p> <p>144</p> | |
| <p>Hepatobiliary disorders</p> <p>hepatic steatosis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>41 / 2791 (1.47%)</p> <p>42</p> | <p>35 / 2800 (1.25%)</p> <p>35</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dermatitis</p> <p>alternative dictionary used: MedDRA 23.0</p> | <p>254 / 2791 (9.10%)</p> <p>266</p> | <p>53 / 2800 (1.89%)</p> <p>53</p> | |

| | | |
|---|--------------------|--------------------|
| subjects affected / exposed | 28 / 2791 (1.00%) | 11 / 2800 (0.39%) |
| occurrences (all) | 31 | 13 |
| dry skin | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 102 / 2791 (3.65%) | 48 / 2800 (1.71%) |
| occurrences (all) | 108 | 51 |
| eczema | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 29 / 2791 (1.04%) | 28 / 2800 (1.00%) |
| occurrences (all) | 32 | 31 |
| erythema | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 38 / 2791 (1.36%) | 26 / 2800 (0.93%) |
| occurrences (all) | 43 | 28 |
| hyperhidrosis | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 29 / 2791 (1.04%) | 32 / 2800 (1.14%) |
| occurrences (all) | 33 | 34 |
| nail disorder | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 43 / 2791 (1.54%) | 4 / 2800 (0.14%) |
| occurrences (all) | 45 | 4 |
| night sweats | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 40 / 2791 (1.43%) | 28 / 2800 (1.00%) |
| occurrences (all) | 43 | 31 |
| onychoclasia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 46 / 2791 (1.65%) | 7 / 2800 (0.25%) |
| occurrences (all) | 54 | 7 |
| pruritus | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 219 / 2791 (7.85%) | 110 / 2800 (3.93%) |
| occurrences (all) | 298 | 121 |

| | | | |
|--|----------------------------|-----------------------------|--|
| rash alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 272 / 2791 (9.75%) 332 | 106 / 2800 (3.79%) 132 | |
| Renal and urinary disorders dysuria alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 46 / 2791 (1.65%) 53 | 25 / 2800 (0.89%) 29 | |
| Endocrine disorders hypothyroidism alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 28 / 2791 (1.00%) 29 | 34 / 2800 (1.21%) 34 | |
| Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 571 / 2791 (20.46%) 705 | 876 / 2800 (31.29%) 1117 | |
| arthritis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 9 / 2791 (0.32%) 10 | 29 / 2800 (1.04%) 33 | |
| back pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 223 / 2791 (7.99%) 277 | 271 / 2800 (9.68%) 317 | |
| bone pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 62 / 2791 (2.22%) 75 | 93 / 2800 (3.32%) 102 | |
| joint range of motion decreased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 24 / 2791 (0.86%) 35 | 29 / 2800 (1.04%) 40 | |

| | | |
|---|--------------------|--------------------|
| joint stiffness | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 22 / 2791 (0.79%) | 56 / 2800 (2.00%) |
| occurrences (all) | 25 | 59 |
| muscle spasms | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 134 / 2791 (4.80%) | 100 / 2800 (3.57%) |
| occurrences (all) | 180 | 121 |
| muscular weakness | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 29 / 2791 (1.04%) | 16 / 2800 (0.57%) |
| occurrences (all) | 31 | 16 |
| musculoskeletal chest pain | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 70 / 2791 (2.51%) | 72 / 2800 (2.57%) |
| occurrences (all) | 77 | 76 |
| musculoskeletal pain | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 111 / 2791 (3.98%) | 154 / 2800 (5.50%) |
| occurrences (all) | 120 | 170 |
| musculoskeletal stiffness | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 32 / 2791 (1.15%) | 33 / 2800 (1.18%) |
| occurrences (all) | 34 | 37 |
| myalgia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 167 / 2791 (5.98%) | 163 / 2800 (5.82%) |
| occurrences (all) | 193 | 185 |
| neck pain | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 48 / 2791 (1.72%) | 59 / 2800 (2.11%) |
| occurrences (all) | 49 | 64 |
| osteopenia | | |
| alternative dictionary used: MedDRA 23.0 | | |

| | | | |
|--|--------------------------------------|--------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>30 / 2791 (1.07%)</p> <p>30</p> | <p>32 / 2800 (1.14%)</p> <p>32</p> | |
| <p>osteoporosis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>45 / 2791 (1.61%)</p> <p>45</p> | <p>71 / 2800 (2.54%)</p> <p>75</p> | |
| <p>pain in extremity</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>245 / 2791 (8.78%)</p> <p>292</p> | <p>274 / 2800 (9.79%)</p> <p>354</p> | |
| <p>Infections and infestations</p> <p>bronchitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>42 / 2791 (1.50%)</p> <p>50</p> | <p>40 / 2800 (1.43%)</p> <p>44</p> | |
| <p>cellulitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>37 / 2791 (1.33%)</p> <p>43</p> | <p>28 / 2800 (1.00%)</p> <p>31</p> | |
| <p>conjunctivitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>55 / 2791 (1.97%)</p> <p>63</p> | <p>30 / 2800 (1.07%)</p> <p>34</p> | |
| <p>gastroenteritis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>73 / 2791 (2.62%)</p> <p>84</p> | <p>32 / 2800 (1.14%)</p> <p>36</p> | |
| <p>herpes zoster</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>34 / 2791 (1.22%)</p> <p>34</p> | <p>39 / 2800 (1.39%)</p> <p>39</p> | |
| <p>influenza</p> <p>alternative dictionary used: MedDRA 23.0</p> | | | |

| | | |
|---|------------------------|--------------------|
| subjects affected / exposed | 110 / 2791 (3.94%) | 102 / 2800 (3.64%) |
| occurrences (all) | 139 | 135 |
| nasopharyngitis | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 231 / 2791 (8.28%) | 186 / 2800 (6.64%) |
| occurrences (all) | 324 | 285 |
| oral herpes | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 29 / 2791 (1.04%) | 8 / 2800 (0.29%) |
| occurrences (all) | 34 | 9 |
| pharyngitis | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 26 / 2791 (0.93%) | 29 / 2800 (1.04%) |
| occurrences (all) | 29 | 33 |
| pneumonia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 45 / 2791 (1.61%) | 19 / 2800 (0.68%) |
| occurrences (all) | 46 | 19 |
| sinusitis | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 69 / 2791 (2.47%) | 51 / 2800 (1.82%) |
| occurrences (all) | 76 | 67 |
| skin infection | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 33 / 2791 (1.18%) | 23 / 2800 (0.82%) |
| occurrences (all) | 36 | 26 |
| upper respiratory tract infection | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 280 / 2791 (10.03%) | 214 / 2800 (7.64%) |
| occurrences (all) | 393 | 323 |
| urinary tract infection | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 278 / 2791 (9.96%) | 167 / 2800 (5.96%) |
| occurrences (all) | 368 | 235 |

| | | | |
|---|-------------------------------|-------------------------|--|
| vaginal infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[16] occurrences (all) | 30 / 2770 (1.08%) 37 | 18 / 2785 (0.65%) 21 | |
| viral infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 28 / 2791 (1.00%) 32 | 14 / 2800 (0.50%) 15 | |
| vulvovaginal candidiasis alternative dictionary used: MedDRA 23.0 subjects affected / exposed ^[17] occurrences (all) | 29 / 2770 (1.05%) 33 | 20 / 2785 (0.72%) 31 | |
| Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 312 / 2791 (11.18%) 352 | 54 / 2800 (1.93%) 57 | |
| dehydration alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 33 / 2791 (1.18%) 39 | 7 / 2800 (0.25%) 7 | |
| hypercalcaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 49 / 2791 (1.76%) 58 | 32 / 2800 (1.14%) 42 | |
| hypercholesterolaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 48 / 2791 (1.72%) 53 | 61 / 2800 (2.18%) 67 | |
| hyperglycaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) | 37 / 2791 (1.33%) 51 | 43 / 2800 (1.54%) 53 | |
| hypertriglyceridaemia alternative dictionary used: MedDRA 23.0 | | | |

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|---|--------------------|-------------------|
| subjects affected / exposed | 67 / 2791 (2.40%) | 45 / 2800 (1.61%) |
| occurrences (all) | 82 | 63 |
| hyperuricaemia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 33 / 2791 (1.18%) | 13 / 2800 (0.46%) |
| occurrences (all) | 44 | 14 |
| hypoalbuminaemia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 30 / 2791 (1.07%) | 12 / 2800 (0.43%) |
| occurrences (all) | 39 | 17 |
| hypokalaemia | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 105 / 2791 (3.76%) | 22 / 2800 (0.79%) |
| occurrences (all) | 126 | 31 |
| vitamin d deficiency | | |
| alternative dictionary used: MedDRA 23.0 | | |
| subjects affected / exposed | 29 / 2791 (1.04%) | 33 / 2800 (1.18%) |
| occurrences (all) | 33 | 37 |

Notes:

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 11 October 2017 | Safety management updates including toxicity dose adjustment guidance for ALT increases; exclusion of participants with a history of venous thromboembolism (VTE); updates to protocol selection criteria to better align with global clinical practice |
| 29 June 2018 | Increase in sample size from 3580 to 4580 participants; exclusion of participants with inflammatory breast cancer; recurrence tissue biomarker sample changed to mandatory for participants that undergo biopsy; updated to collect SAEs in both arms regardless of causality or relatedness through year 5; added section on safety monitoring for VTE |
| 19 December 2018 | Updated the ITT population to include participants in Cohort 1 and Cohort 2; modified VTE safety monitoring language including the addition of Appendix 12 guidance for management of VTE while on study; included AST in the hepatic function safety monitoring; number of events required at final IDFS was updated from approximately 345 to approximately 390 from across Cohort 1 and Cohort 2 to yield approximately 85% statistical power |
| 25 June 2019 | Update on the timing of the efficacy interim analyses to ensure the data are sufficiently mature; added interstitial lung disease (ILD)/pneumonitis as a new adverse drug reaction; added safety monitoring guidance related to ILD/pneumonitis |
| 18 September 2019 | Changed protocol language from 'capsules' to 'tablets or capsules' to allow for supply chain planning in the event the study switches from capsules formulation to tablets |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported