



Clinical trial results:

Open Label, Multinational, Multicenter, Real-World Treatment Study of Single Agent AZD9291 for Patients with Advanced/Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Prior Therapy with an EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2015-001407-31 |
| Trial protocol | SE BE IT AT DK ES IE |
| Global end of trial date | 18 April 2019 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 28 August 2021 |
| First version publication date | 28 August 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D5160C00022 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02474355 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 151 85 |
| Public contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 February 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 April 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of single agent AZD9291 in a real world setting in adult patients with advanced or metastatic, epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-tyrosine kinase inhibitor (TKI) therapy.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 18 September 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 30 |
| Country: Number of subjects enrolled | Australia: 31 |
| Country: Number of subjects enrolled | Austria: 46 |
| Country: Number of subjects enrolled | Belgium: 31 |
| Country: Number of subjects enrolled | Brazil: 88 |
| Country: Number of subjects enrolled | Canada: 99 |
| Country: Number of subjects enrolled | China: 1350 |
| Country: Number of subjects enrolled | Denmark: 6 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Italy: 510 |
| Country: Number of subjects enrolled | Saudi Arabia: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 466 |
| Country: Number of subjects enrolled | Spain: 131 |
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | Taiwan: 188 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Worldwide total number of subjects | 3014 |
| EEA total number of subjects | 741 |

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) | 1798 |
| From 65 to 84 years | 1185 |
| 85 years and over | 31 |

Subject disposition

Recruitment

Recruitment details:

Participants who met all the inclusion and none of the exclusion criteria received treatment in a total of 209 centres in 16 countries. The study started on 18 September 2015 and primary completion date was 18 April 2019.

Pre-assignment

Screening details:

During the screening period (28 days), eligible participants signed the informed consent. All the study assessments were performed as per the schedule of assessment.

Period 1

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

Arms

| | |
|-----------|-------------|
| Arm title | Osimertinib |
|-----------|-------------|

Arm description:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities)

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Osimertinib |
| Investigational medicinal product code | |
| Other name | AZD9291 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities).

| Number of subjects in period 1 | Osimertinib |
|------------------------------------|-------------|
| Started | 3014 |
| Completed | 1386 |
| Not completed | 1628 |
| Consent withdrawn by subject | 124 |
| Eligibility Criteria not Fulfilled | 2 |
| Other | 43 |
| Death | 1361 |
| Lost to follow-up | 98 |

Baseline characteristics

Reporting groups

| | |
|--|-------------|
| Reporting group title | Osimertinib |
| Reporting group description: | |
| All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities) | |

| Reporting group values | Osimertinib | Total | |
|---|-------------|-------|--|
| Number of subjects | 3014 | 3014 | |
| Age Categorical | | | |
| Units: Participants | | | |
| <=18 years | 0 | 0 | |
| Between 18 and 65 years | 1798 | 1798 | |
| >=65 years | 1216 | 1216 | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 61.7 | | |
| standard deviation | ± 10.91 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 1927 | 1927 | |
| Male | 1087 | 1087 | |
| Country | | | |
| Units: Subjects | | | |
| Argentina | 30 | 30 | |
| Australia | 31 | 31 | |
| Austria | 46 | 46 | |
| Belgium | 31 | 31 | |
| Brazil | 88 | 88 | |
| Canada | 99 | 99 | |
| China | 1350 | 1350 | |
| Denmark | 6 | 6 | |
| Ireland | 10 | 10 | |
| Italy | 510 | 510 | |
| Saudi Arabia | 3 | 3 | |
| South Korea | 466 | 466 | |
| Spain | 131 | 131 | |
| Sweden | 7 | 7 | |
| Taiwan | 188 | 188 | |
| United Kingdom | 18 | 18 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 2085 | 2085 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 21 | 21 | |
| White | 897 | 897 | |

| | | | |
|-------------------------|----|----|--|
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 11 | 11 | |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Osimertinib |
| Reporting group description: All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities) | |

Primary: Overall Survival (OS)

| | |
|---|--------------------------------------|
| End point title | Overall Survival (OS) ^[1] |
| End point description: OS was defined as the time, in months from the date of first dose of Osimertinib until death due to any cause, or at last documented contact with participant status "alive" (in this study any participants alive at study discontinuation, or lost to follow-up was considered being censored at study discontinuation date or at the last known date participant was alive). OS was summarized using a Kaplan-Meier (KM) estimate of the median time to death or censoring together with their 95% confidence intervals. | |
| End point type | Primary |
| End point timeframe: From the date of first dose of Osimertinib until the date of death (due to any cause) or last participant contact [up to 43 months] | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical tests were performed, the statistical analyses were descriptive. | |

| End point values | Osimertinib | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3014 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 22.8 (21.6 to 23.8) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with serious adverse events (SAEs), AEs leading to dose modification, AEs leading to discontinuation, AEs of special interest (AESIs)

| | |
|--|---|
| End point title | Number of participants with serious adverse events (SAEs), AEs leading to dose modification, AEs leading to discontinuation, AEs of special interest (AESIs) ^[2] |
| End point description: Safety assessment of Osimertinib was analyzed by evaluating SAEs, AEs leading to dose modification, AEs leading to discontinuation, AESIs. | |
| End point type | Primary |
| End point timeframe: From screening to progression follow-up [every 6 weeks (\pm 1 week) relative to the date of enrolment until end of study] | |

Notes:

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

Justification: No statistical tests were performed, the statistical analyses were descriptive.

| End point values | Osimertinib | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3014 | | | |
| Units: Participants | | | | |
| AE of special interest (AESI) or SAE | 923 | | | |
| AESI or SAE a causally related to Osimertinib | 338 | | | |
| AE leading to dose modification | 414 | | | |
| AE leading to discontinuation | 191 | | | |
| AESI | 113 | | | |
| AESI causally related to Osimertinib | 89 | | | |
| SAE | 657 | | | |
| SAE causally related to Osimertinib | 95 | | | |
| AE leading to death | 152 | | | |
| AE leading to death related to Osimertinib | 19 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

| | |
|--|---------------------------|
| End point title | Progression free survival |
| End point description: | |
| PFS was defined as the time, in months from first dose of Osimertinib until the date of disease progression or death in the absence of progression. Participants who had not progressed or died at study discontinuation were censored at the time of the latest date of disease assessment. PFS was summarized using KM estimates of the median time to progression or death with their 95% confidence intervals. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months] | |

| End point values | Osimertinib | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3014 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.1 (11.0 to 12.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Discontinuation (TTD)

| | |
|-----------------|---|
| End point title | Time to Treatment Discontinuation (TTD) |
|-----------------|---|

End point description:

TTD or death was assessed as a supportive summary to PFS and defined as the time from the date of the first dose of osimertinib in the study until the date of osimertinib discontinuation or death, regardless of the reason for discontinuation. TTD was summarized using KM estimates of the median times to progression or death or treatment discontinuation.

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

End point timeframe:

From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months]

| End point values | Osimertinib | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3014 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 13.5 (12.6 to 13.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate (RR)

| | |
|-----------------|--------------------|
| End point title | Response rate (RR) |
|-----------------|--------------------|

End point description:

RR was defined as the number (%) of participants with a best response (by Investigator assessment) of 'responding', regardless of the method of evaluation, and was based on a subset of the full analysis set consisting of subjects with at least one documented response assessment. RR was summarised together with the 95% CI.

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

End point timeframe:

From the date of first dose of Osimertinib until disease progression or death in the absence of progression [up to 43 months]

| End point values | Osimertinib | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3014 | | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 57.3 (55.5 to 59.2) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to progression follow-up [every 6 weeks (\pm 1 week) relative to the date of enrolment until end of study]

Adverse event reporting additional description:

Safety of AZD9291 by assessment of SAEs, AEs of special interest (AESI) [Interstitial Lung Disease/pneumonitis-like events, and QTc prolongation events].

This study did not collect all AEs; only SAEs, adverse events leading to dose modification, adverse events leading to treatment discontinuation and AESI were collected.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Osimertinib |
|-----------------------|-------------|

Reporting group description:

All participants received oral 80 mg tablet once a day (the dose could be reduced to 40 mg for management of osimertinib-related toxicities).

| Serious adverse events | Osimertinib | | |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 657 / 3014 (21.80%) | | |
| number of deaths (all causes) | 1361 | | |
| number of deaths resulting from adverse events | 19 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|--|------------------|--|--|--|
| Acute promyelocytic leukaemia subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Benign breast neoplasm subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder cancer recurrent subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder neoplasm subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder transitional cell carcinoma subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast cancer female subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Glioblastoma subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to bone subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastases to central nervous system | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal cancer | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cancer metastatic | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 17 / 3014 (0.56%) | | |
| occurrences causally related to treatment / all | 2 / 18 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava occlusion | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vena cava thrombosis | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Unintended pregnancy | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 34 / 3014 (1.13%) | | |
| occurrences causally related to treatment / all | 1 / 34 | | |
| deaths causally related to treatment / all | 1 / 34 | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 3014 (0.40%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Sudden death | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Condition aggravated | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cyst | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Granuloma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-------------------|--|--|
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometrial hyperplasia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostatic obstruction | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 49 / 3014 (1.63%) | | |
| occurrences causally related to treatment / all | 5 / 49 | | |
| deaths causally related to treatment / all | 3 / 13 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 20 / 3014 (0.66%) | | |
| occurrences causally related to treatment / all | 1 / 25 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-------------------|--|--|--|
| Dyspnoea | | | | |
| subjects affected / exposed | 15 / 3014 (0.50%) | | | |
| occurrences causally related to treatment / all | 2 / 15 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 11 / 3014 (0.36%) | | | |
| occurrences causally related to treatment / all | 2 / 11 | | | |
| deaths causally related to treatment / all | 2 / 9 | | | |
| Interstitial lung disease | | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | | |
| occurrences causally related to treatment / all | 7 / 9 | | | |
| deaths causally related to treatment / all | 3 / 4 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | | |
| occurrences causally related to treatment / all | 6 / 9 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Asphyxia | | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Pneumothorax | | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Bronchitis chronic | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cough | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchial haemorrhage | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute interstitial pneumonitis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Asthma | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchiectasis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Emphysema | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Delirium | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breath holding | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 3 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase | | | |

| | | | |
|--|------------------|--|--|
| increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eastern Cooperative Oncology Group performance status worsened | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza A virus test | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 8 / 3014 (0.27%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|------------------|--|--|--|
| Lumbar vertebral fracture | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal fracture | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Traumatic fracture | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple injuries | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subdural haematoma | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thoracic vertebral fracture | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain herniation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Compression fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foreign body in respiratory tract | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic fracture | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulna fracture | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulnar nerve injury | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 10 | | |
| deaths causally related to treatment / all | 1 / 3 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure acute | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiomyopathy | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Palpitations | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericardial effusion | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Arrhythmia | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorder | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac dysfunction | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiopulmonary failure | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiotoxicity | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Congestive cardiomyopathy | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Hypertensive heart disease | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial ischaemia | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sinus tachycardia | | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 22 / 3014 (0.73%) | | |
| occurrences causally related to treatment / all | 5 / 22 | | |
| deaths causally related to treatment / all | 2 / 11 | | |
| Headache | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Epilepsy | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Lacunar infarction | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cognitive disorder | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Generalised tonic-clonic seizure | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhage intracranial | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhagic stroke | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Apraxia | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Basal ganglia infarction | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brain oedema | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebellar ischaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorder | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychomotor skills impaired | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombotic stroke | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular headache | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myelosuppression | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia of chronic disease | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood disorder | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Middle ear inflammation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dacryostenosis acquired | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|-------------------|--|--|--|
| Vomiting | | | | |
| subjects affected / exposed | 13 / 3014 (0.43%) | | | |
| occurrences causally related to treatment / all | 0 / 16 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 12 / 3014 (0.40%) | | | |
| occurrences causally related to treatment / all | 6 / 12 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Nausea | | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Abdominal pain | | | | |
| subjects affected / exposed | 7 / 3014 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enteritis | | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ascites | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic gastritis | | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulum intestinal haemorrhagic | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastric perforation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal perforation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gingival ulceration | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematochezia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ischaemic enteritis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Obstructive pancreatitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peptic ulcer | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peptic ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biliary colic | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver injury | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic foot | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Haematuria | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urinary | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal injury | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 7 / 3014 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | | |
|---|------------------|--|--|--|
| Arthralgia | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intervertebral disc protrusion | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoporotic fracture | | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bone pain | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fracture pain | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant psoas syndrome | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myopathy | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myositis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteoporosis | | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Synovitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spondylolisthesis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vertebral lesion | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 74 / 3014 (2.46%) | | |
| occurrences causally related to treatment / all | 7 / 79 | | |
| deaths causally related to treatment / all | 4 / 20 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 10 / 3014 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract infection | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 10 / 3014 (0.33%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 7 / 3014 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urosepsis | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Device related infection | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Emphyema | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Complicated appendicitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis infectious | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhagic fever | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterobacter pneumonia | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infectious pleural effusion | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective spondylitis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Labyrinthitis | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngitis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Localised infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection bacterial | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphangitis | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis aseptic | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mucosal infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nasal abscess | | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Otitis media acute | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral nerve infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumocystis jirovecii pneumonia | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia fungal | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postoperative wound infection | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Scrub typhus | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection bacterial | | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 8 / 3014 (0.27%) | | |
| occurrences causally related to treatment / all | 2 / 11 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences causally related to treatment / all | 4 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Cachexia | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Osimertinib | | |
|---|---------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 380 / 3014 (12.61%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Lymphangiosis carcinomatosa | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 3014 (0.23%) | | |
| occurrences (all) | 7 | | |
| Asthenia | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 8 / 3014 (0.27%) | | |
| occurrences (all) | 8 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences (all) | 5 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences (all) | 4 | | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Reproductive system and breast disorders | | | |
| Testicular cyst | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 13 / 3014 (0.43%) | | |
| occurrences (all) | 14 | | |
| Cough | | | |

| | | | |
|---------------------------------------|-------------------|--|--|
| subjects affected / exposed | 4 / 3014 (0.13%) | | |
| occurrences (all) | 4 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 3 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Pulmonary toxicity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 10 / 3014 (0.33%) | | |
| occurrences (all) | 11 | | |
| Platelet count decreased | | | |

| | | | |
|--|-------------------|--|--|
| subjects affected / exposed | 17 / 3014 (0.56%) | | |
| occurrences (all) | 25 | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 88 / 3014 (2.92%) | | |
| occurrences (all) | 122 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 10 / 3014 (0.33%) | | |
| occurrences (all) | 14 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | |
| occurrences (all) | 10 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | |
| occurrences (all) | 12 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 8 / 3014 (0.27%) | | |
| occurrences (all) | 8 | | |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 4 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Blood bilirubin increased | | | |

| | | | |
|---|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Blood pressure systolic increased subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hepatic enzyme increased subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Lipase increased subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 3 | | |
| Transaminases increased subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Injury, poisoning and procedural complications Radiation pneumonitis subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Chemical burns of eye subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Corneal abrasion subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Cardiac disorders Sinus bradycardia subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Atrioventricular block first degree subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Atrial fibrillation | | | |

| | | | |
|--------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Extrasystoles | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Bundle branch block left | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Nodal rhythm | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Supraventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences (all) | 3 | | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Demyelination | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Facial nerve disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Psychomotor skills impaired | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 20 / 3014 (0.66%) | | |
| occurrences (all) | 22 | | |
| Neutropenia | | | |
| subjects affected / exposed | 16 / 3014 (0.53%) | | |
| occurrences (all) | 24 | | |
| Myelosuppression | | | |

| | | | |
|--|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 6 / 3014 (0.20%) 8 | | |
| Anaemia subjects affected / exposed occurrences (all) | 5 / 3014 (0.17%) 6 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 3 / 3014 (0.10%) 4 | | |
| Pancytopenia subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Blepharitis subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Ulcerative keratitis subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Dry eye subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Swelling of eyelid subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Visual acuity reduced | | | |

| | | | |
|---------------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Vitreoretinal traction syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 11 / 3014 (0.36%) | | |
| occurrences (all) | 12 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 30 / 3014 (1.00%) | | |
| occurrences (all) | 37 | | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 3014 (0.33%) | | |
| occurrences (all) | 14 | | |
| Stomatitis | | | |
| subjects affected / exposed | 9 / 3014 (0.30%) | | |
| occurrences (all) | 10 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Anal inflammation | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-------------------------|--|--|
| Mouth ulceration subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Lip swelling subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Rectal haemorrhage subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all) | 3 / 3014 (0.10%) 3 | | |
| Drug-induced liver injury subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hepatotoxicity subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hypertransaminaemia subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 2 | | |
| Liver injury subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 10 / 3014 (0.33%) 11 | | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 6 / 3014 (0.20%) 6 | | |
| Skin toxicity | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences (all) | 1 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences (all) | 7 | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences (all) | 4 | | |
| Nail disorder | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Eczema asteatotic | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Onycholysis | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Skin reaction | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------------|--|--|
| Skin ulcer subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Renal and urinary disorders | | | |
| Azotaemia subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Renal impairment subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Hydronephrosis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Proteinuria subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 2 | | |
| Nephropathy toxic subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Renal disorder subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Hypercreatinaemia subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Arthralgia | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 7 / 3014 (0.23%) | | |
| occurrences (all) | 9 | | |
| Paronychia | | | |
| subjects affected / exposed | 11 / 3014 (0.36%) | | |
| occurrences (all) | 11 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 6 / 3014 (0.20%) | | |
| occurrences (all) | 6 | | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 3014 (0.17%) | | |
| occurrences (all) | 5 | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |
| Cystitis | | | |
| subjects affected / exposed | 2 / 3014 (0.07%) | | |
| occurrences (all) | 2 | | |

| | | | |
|--|-----------------------|--|--|
| Gastroenteritis viral subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Herpes ophthalmic subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Pneumonia viral subjects affected / exposed occurrences (all) | 2 / 3014 (0.07%) 2 | | |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Cellulitis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Gingivitis subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Oral herpes subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 3014 (0.03%) 1 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 5 / 3014 (0.17%) 5 | | |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 3 / 3014 (0.10%) | | |
| occurrences (all) | 3 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Abnormal loss of weight | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3014 (0.03%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 30 June 2015 | <ul style="list-style-type: none">- Patient recruitment was expanded to other regions (America and Asia), a clause about study termination in each country was added and procedures for discontinuation of a subject from study treatment were added, details about what will happen in case of study withdrawal and follow up of overall survival were added, the study plan (Table 4) was amended to provide more details in line with the CRF and more details about the enrolment process, clarification about T790M testing and what will happen to the samples if a central laboratory is used.- Male patient contraception was clarified.- Details regarding QTc prolongation and identity and dose of investigational product were aligned to the core data sheet.- The statistical methods and analysis included a more robust description of statistical evaluations and sample size determination. |
| 23 June 2016 | <ul style="list-style-type: none">- The number of patients enrolled was revised in Europe from 1500 to 600 due to lower enrolment than initially planned. The total enrolment was more defined as approximately 3500 with the participation of China.- The data collection is to stop at last patient last visit due to the removal of the patient registry after national reimbursement.- The primary efficacy outcome was clarified as overall survival, the secondary efficacy outcomes were clarified as investigator assessed response rate, investigator assessed progression free survival and time to treatment discontinuation.- Definition for response rate and time to treatment discontinuation was added.- The exclusion criteria relating to patients being excluded due to evidence of an active infection was clarified with a definition for active infection.- An interim analysis of the global data was added to take place annually for the first 3 years.- A steering committee was added for oversight and supervision of the study. |
| 20 October 2016 | <ul style="list-style-type: none">- Details were added regarding an addendum to the informed consent form to be signed and dated to enable the collection of images (CT scans or MRI) from a selected subset of patients for independent central analysis by an AstraZeneca appointed CRO.- Table 4 (footnote c) was amended to clarify the 30 days post last follow up contact is by a visit or by telephone (for new/ongoing serious adverse events (SAEs) and adverse events of special interest.- Details regarding definition and management of overdose were added and it was clarified that all overdose data (not just those relating to an SAE) should be reported to AstraZeneca with details of the process. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|----------------|---|--------------|
| 08 August 2018 | Delay to database lock due to needing a further approval to consent patients and collect scans in one of the participating countries. | - |

Notes:

Limitations and caveats

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

Participants alive at the time of national reimbursement or site closure were no longer followed for survival and therefore prematurely censored for the OS, PFS, and TTD analysis, leading to less mature data.

Notes: