# Clinical trial results:
# A Phase 1/2, Open-Label, Safety, Pharmacokinetic and Preliminary Efficacy Study of Oral CO-1686 in Patients with Previously Treated Mutant EGFR Non-small Cell Lung Cancer (NSCLC)

## Summary

| | |
|---|---|
| EudraCT number | 2011-005215-86 |
| Trial protocol | PL |
| Global end of trial date | 27 August 2018 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 09 March 2020 |
| First version publication date | 04 July 2019 |
| Version creation reason | • New data added to full data set<br>New data is available for primary outcomes DOR and DLT incidence, and for secondary outcomes OS, PFS and PK. |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CO-1686-008 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01526928 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Clovis Oncology UK Ltd |
| Sponsor organisation address | Granta Centre, Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GP |
| Public contact | Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 12233645500, lrolfe@clovisoncology.com |
| Scientific contact | Dr Lindsey Rolfe, Clovis Oncology UK Ltd, +44 12233645500, lrolfe@clovisoncology.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 | 27 August 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 July 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 August 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Phase 1:
To evaluate the toxicity profile of escalating doses of CO-1686 and to determine the MTD and RP2D
To characterize the PK profile of CO-1686

Phase 2:
To evaluate tumor response (ORR + duration of response) to CO-1686 in patients with T790M

Protection of trial subjects:

Safety measures in Phase 1 included monitoring for dose limiting toxicities (DLTs), as specified in the protocol, that occurred during Cycle 1 in patients enrolled into a DLT-evaluable cohort and were assessed by the investigator as probably, possibly or definitively related to rociletinib, as well as monitoring for adverse events (AEs). Safety measures in Phase 2 included monitoring of AEs, clinical laboratory evaluations, physical examination, vital signs and body weight, 12-lead ECGs, ECOG performance status, and concomitant medications and procedures. Patients were monitored for AEs from the time the first dose of rociletinib was administered through 28 days after the last dose (End of Treatment Visit), including study procedure-related AEs that occurred after signing of the informed consent and before administration of rociletinib. Any ongoing serious AEs were followed until resolution or stabilization. Quality of Life assessments were performed at baseline, every 2 cycles through Cycle 6, and then every 3 cycles thereafter.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 March 2012 |
| 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 | Poland: 5 |
| Country: Number of subjects enrolled | France: 61 |
| Country: Number of subjects enrolled | Australia: 28 |
| Country: Number of subjects enrolled | United States: 518 |
| Worldwide total number of subjects | 612 |
| EEA total number of subjects | 66 |

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) | 327 |
| From 65 to 84 years | 272 |
| 85 years and over | 13 |

## Subject disposition

### Recruitment

Recruitment details:

There were 612 patients who received rociletinib—111 enrolled in Phase 1 and 501 enrolled in Phase 2. The Phase 1 component of the study was conducted at 8 study sites in the US, Australia, and France. Phase 2 was conducted at 49 study sites in the US, France, Poland, and Australia.

### Pre-assignment

Screening details:

Phase 1 - Eligible patients were required to have documented evidence of an EGFR-activating mutation, but enrollment into Phase 1 was irrespective of T790M status. Phase 2 - Eligible patients were those who were confirmed by the sponsor's central laboratory or by local assessment to have the T790M mutation in tumor tissue.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Rociletinib <900 mg BID FB Capsules |

Arm description:

Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rociletinib free base (FB) capsules |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib free base (FB) capsule doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID). This arm also includes a 400 mg three times a day (TID) dose. Rociletinib free base (FB) capsules were administered in Phase 1 only (until November 2013) and were provided in 50 mg or 150 mg white capsules. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day treatment cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| | |
|---|---|
| **Arm title** | Rociletinib 900 mg BID FB Capsules |

Arm description:

Rociletinib free base (FB) dose 900 mg twice a day (BID)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rociletinib free base (FB) capsules |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib free base (FB) dose 900 mg twice a day (BID). Rociletinib FB capsules were administered in

Phase 1 only (until November 2013) and were provided in 50 mg or 150 mg white capsules. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day treatment cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| **Arm title** | Rociletinib 500 mg BID HBr Tablets |
|---|---|

Arm description:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rociletinib hydrobromide (HBr) tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after ameal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| **Arm title** | Rociletinib 625 mg BID HBr Tablets |
|---|---|

Arm description:

Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rociletinib hydrobromide (HBr) tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 625 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after ameal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| **Arm title** | Rociletinib 750 mg BID HBr Tablets |
|---|---|

Arm description:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)

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

| | |
|---|---|
| Investigational medicinal product name | Rociletinib hydrobromide (HBr) tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| | |
|---|---|
| **Arm title** | Rociletinib 1000 mg BID HBr Tablets |

Arm description:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rociletinib hydrobromide (HBr) tablets |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID). Rociletinib hydrobromide (HBr) tablets were administered in Phase 1 (starting in August 2013) and in all Phase 2 cohorts and were provided as 125 mg (round) or 250 mg (oval) yellow tablets. Patients were instructed to take each dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Patients received rociletinib in 21-day cycles and were treated until there was progression by RECIST v1.1, clinical tumor progression, or unacceptable toxicity, or other discontinuation criteria were met. Patients could opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if the patient provided consent, and the investigator and sponsor approved.

| **Number of subjects in period 1** | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets |
|---|---|---|---|
| Started | 38 | 19 | 209 |
| Completed | 0 | 0 | 0 |
| Not completed | 38 | 19 | 209 |
| Consent withdrawn by subject | 1 | - | 13 |
| Physician decision | - | - | 2 |
| Adverse Event | 2 | 1 | 29 |
| Death | - | - | 3 |
| Progressive Disease | 35 | 17 | 150 |
| Unknown | - | 1 | 11 |
| Lost to follow-up | - | - | - |
| Missing | - | - | 1 |

| | | | |
|---|---|---|---|
| Protocol deviation | - | - | - |

| **Number of subjects in period 1** | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets |
|---|---|---|---|
| Started | 245 | 95 | 6 |
| Completed | 0 | 0 | 0 |
| Not completed | 245 | 95 | 6 |
| Consent withdrawn by subject | 11 | 3 | - |
| Physician decision | 5 | - | - |
| Adverse Event | 40 | 13 | 2 |
| Death | - | - | - |
| Progressive Disease | 182 | 76 | 4 |
| Unknown | 4 | 1 | - |
| Lost to follow-up | 1 | - | - |
| Missing | - | 2 | - |
| Protocol deviation | 2 | - | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Rociletinib <900 mg BID FB Capsules |
| Reporting group description: | |
| Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID). | |
| Reporting group title | Rociletinib 900 mg BID FB Capsules |
| Reporting group description: | |
| Rociletinib free base (FB) dose 900 mg twice a day (BID) | |
| Reporting group title | Rociletinib 500 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID) | |
| Reporting group title | Rociletinib 625 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID) | |
| Reporting group title | Rociletinib 750 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID) | |
| Reporting group title | Rociletinib 1000 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID) | |

| Reporting group values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets |
|---|---|---|---|
| Number of subjects | 38 | 19 | 209 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 60.1 | 58.9 | 63.6 |
| standard deviation | ± 11.54 | ± 8.37 | ± 11.45 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 31 | 15 | 155 |
| Male | 7 | 4 | 54 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | 2 | 5 |
| Not Hispanic or Latino | 30 | 15 | 170 |
| Unknown or Not Reported | 6 | 2 | 34 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 5 | 4 | 41 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 4 |

| | | | |
|---|---|---|---|
| Black or African American | 0 | 0 | 7 |
| White | 27 | 13 | 122 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 6 | 2 | 35 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 27 | 13 | 122 |
| Black or African American | 0 | 0 | 7 |
| Asian | 5 | 4 | 41 |
| Other | 6 | 2 | 39 |
| T790M Status (Determined by Central Lab)<br>Units: Subjects | | | |
| Negative | 5 | 4 | 6 |
| Positive | 23 | 9 | 188 |
| Unknown | 10 | 6 | 4 |
| Missing | 0 | 0 | 11 |
| History of CNS Metastases<br>Units: Subjects | | | |
| Yes | 20 | 7 | 86 |
| No | 18 | 12 | 123 |
| Time Since Diagnosis of NSCLC<br>Units: months | | | |
| arithmetic mean | 40.4 | 45.4 | 36.7 |
| standard deviation | ± 29.2 | ± 31.94 | ± 25.81 |
| Number of Previous Therapies<br>Units: Therapies | | | |
| arithmetic mean | 3.8 | 3.7 | 2.6 |
| standard deviation | ± 1.65 | ± 1.66 | ± 1.74 |
| Number of Previous TKI Therapies<br>Units: Therapies | | | |
| arithmetic mean | 1.7 | 2.3 | 1.5 |
| standard deviation | ± 0.77 | ± 1.48 | ± 0.87 |

| **Reporting group values** | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets |
|---|---|---|---|
| Number of subjects | 245 | 95 | 6 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 62.5 | 61.5 | 65.2 |
| standard deviation | ± 11.14 | ± 11.82 | ± 5.53 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 155 | 63 | 5 |
| Male | 90 | 32 | 1 |

| | | | |
|---|---|---|---|
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 14 | 2 | 0 |
| Not Hispanic or Latino | 184 | 90 | 6 |
| Unknown or Not Reported | 47 | 3 | 0 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 0 |
| Asian | 49 | 24 | 1 |
| Native Hawaiian or Other Pacific Islander | 3 | 0 | 0 |
| Black or African American | 8 | 2 | 0 |
| White | 137 | 64 | 5 |
| More than one race | 1 | 0 | 0 |
| Unknown or Not Reported | 46 | 5 | 0 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 137 | 64 | 5 |
| Black or African American | 8 | 2 | 0 |
| Asian | 49 | 24 | 1 |
| Other | 51 | 5 | 0 |
| T790M Status (Determined by Central Lab)<br>Units: Subjects | | | |
| Negative | 25 | 9 | 0 |
| Positive | 176 | 80 | 4 |
| Unknown | 1 | 1 | 2 |
| Missing | 43 | 5 | 0 |
| History of CNS Metastases<br>Units: Subjects | | | |
| Yes | 107 | 44 | 3 |
| No | 138 | 51 | 3 |
| Time Since Diagnosis of NSCLC<br>Units: months | | | |
| arithmetic mean | 36.7 | 37.6 | 47.4 |
| standard deviation | ± 31.41 | ± 29.97 | ± 27.03 |
| Number of Previous Therapies<br>Units: Therapies | | | |
| arithmetic mean | 2.8 | 2.9 | 3.8 |
| standard deviation | ± 1.91 | ± 2.11 | ± 2.04 |
| Number of Previous TKI Therapies<br>Units: Therapies | | | |
| arithmetic mean | 1.6 | 1.6 | 1.8 |
| standard deviation | ± 0.77 | ± 0.86 | ± 0.75 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 612 | | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 424 | | |
| Male | 188 | | |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 25 | | |
| Not Hispanic or Latino | 495 | | |
| Unknown or Not Reported | 92 | | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 1 | | |
| Asian | 124 | | |
| Native Hawaiian or Other Pacific Islander | 7 | | |
| Black or African American | 17 | | |
| White | 368 | | |
| More than one race | 1 | | |
| Unknown or Not Reported | 94 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 368 | | |
| Black or African American | 17 | | |
| Asian | 124 | | |
| Other | 103 | | |
| T790M Status (Determined by Central Lab)<br>Units: Subjects | | | |
| Negative | 49 | | |
| Positive | 480 | | |
| Unknown | 24 | | |
| Missing | 59 | | |
| History of CNS Metastases<br>Units: Subjects | | | |
| Yes | 267 | | |
| No | 345 | | |
| Time Since Diagnosis of NSCLC<br>Units: months<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Number of Previous Therapies<br>Units: Therapies<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Number of Previous TKI Therapies<br>Units: Therapies<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Rociletinib <900 mg BID FB Capsules |
| Reporting group description: | |
| Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID). | |
| Reporting group title | Rociletinib 900 mg BID FB Capsules |
| Reporting group description: | |
| Rociletinib free base (FB) dose 900 mg twice a day (BID) | |
| Reporting group title | Rociletinib 500 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID) | |
| Reporting group title | Rociletinib 625 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID) | |
| Reporting group title | Rociletinib 750 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID) | |
| Reporting group title | Rociletinib 1000 mg BID HBr Tablets |
| Reporting group description: | |
| Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID) | |
| Subject analysis set title | Rociletinib 150 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 150 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 200 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 200 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 300 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 300 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 450 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 450 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 600 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 600 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 900 mg QD FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 900 mg once a day (QD) | |
| Subject analysis set title | Rociletinib 100 mg BID FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 100 mg twice a day (BID) | |
| Subject analysis set title | Rociletinib 300 mg BID FB Capsules |

| | |
|---|---|
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 300 mg twice a day (BID) | |
| Subject analysis set title | Rociletinib 600 mg BID FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 600 mg twice a day (BID) | |
| Subject analysis set title | Rociletinib 400 mg TID FB Capsules |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Rociletinib free base (FB) dose 400 mg three times a day (TID) | |

## Primary: Percentage of T790M Positive Patients With Confirmed Response Per Investigator

| | |
|---|---|
| End point title | Percentage of T790M Positive Patients With Confirmed Response Per Investigator[1] |

End point description:

Percentage of patients with a T790M mutation (determined by central lab) with a best overall confirmed response of partial response (PR) or complete response (CR) recorded from the start of the treatment until disease progression or recurrence. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions, defined by and assessed as: Complete Response (CR), is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial Response (PR), at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter. Analysis Population Description - Intent-to-treat: All randomized patients who are confirmed by central lab to be T790M positive.

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

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 42 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: Per EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, all statistical analyses details are provided in the End point values sections.

| End point values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23[2] | 9[3] | 188[4] | 176[5] |
| Units: Percentage of Patients | 0 | 33 | 29 | 41 |

Notes:

[2] - 0/23 = 0.0%; 95% Confidence Interval = 0.0 - 14.8%

[3] - 3/9 = 33.3%; 95% Confidence Interval = 7.5 - 70.1%

[4] - 54/188 = 28.7%; 95% Confidence Interval = 22.4 - 35.8%

[5] - 72/176 = 40.9%; 95% Confidence Interval = 33.6 - 48.6%

| End point values | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80[6] | 4[7] | | |
| Units: Percentage of Patients | 29 | 75 | | |

Notes:

[6] - 23/80 = 28.8%; 95% Confidence Interval = 19.2 - 40.0%

[7] - 3/4 = 75.0%; 95% Confidence Interval = 19.4 - 99.4%

## Statistical analyses

No statistical analyses for this end point

## Primary: Duration of Response (DOR) in T790M Positive Patients According to RECIST Version 1.1 as Determined by Investigator Assessment

| End point title | Duration of Response (DOR) in T790M Positive Patients According to RECIST Version 1.1 as Determined by Investigator Assessment[8][9] |
|---|---|

End point description:

Duration of Response in patients with a T790M mutation (determined by central lab) with confirmed response per investigator. The DOR for complete response (CR) and partial response (PR) was measured from the date that any of these best responses is first recorded until the first date that progressive disease (PD) is objectively documented. For patients who continue treatment post-progression, the first date of progression was used for the analysis. Analysis Population Description: The DOR was measured only in T790M positive patients with a Complete Response (CR) or Partial Response (PR). There were no responders in the Rociletinib <900 mg BID treatment group so DOR is not applicable and thus not reported.

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

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 36 months

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per EMA feedback, the statistical analyses section can not accommodate the end point results for this study. Therefore, all statistical analyses details are provided in the End point values sections.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There were no responders in the Rociletinib <900 mg BID treatment group so DOR is not applicable and thus not reported.

| **End point values** | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3[10] | 54[11] | 72[12] | 23[13] |
| Units: Median DOR in Days | 329 | 275 | 274 | 217 |

Notes:

[10] - Median (95% Confidence Interval) = 329 days (190 to 713)

[11] - Median (95% Confidence Interval) = 275 days (226 to 336)

[12] - Median (95% Confidence Interval) = 274 days (169 to 337)

[13] - Median (95% Confidence Interval) = 217 days (146 to 340)

| **End point values** | Rociletinib 1000 mg BID HBr Tablets | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3[14] | | | |
| Units: Median DOR in Days | 428 | | | |

Notes:

[14] - Median (95% Confidence Interval) = 428 days (NA to NA*) *insufficient number of participants for CI

## Statistical analyses

No statistical analyses for this end point

## Primary: Dose Limiting Toxicity (DLT) Incidence

| End point title | Dose Limiting Toxicity (DLT) Incidence[15] |
|---|---|

End point description:

The number of Phase 1 patients who experienced dose limiting toxicities after one cycle (21 days) of study drug. Since an MTD was never reached for any of the rociletinib FB or HBr formulations/doses, a 750 mg BID HBr starting dose was selected based on early efficacy data from Phase 1, and enrollment into Phase 2 was initiated at this dosage. As the Phase 1 efficacy data matured, the recommended dose was adjusted to 625 mg BID based on antitumor activity and safety evaluations.

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

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 21

Notes:

[15] - 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: There is no statistical analyses for this primary endpoint.

| End point values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 24 | 6 | 6 | 8 |
| Units: Participants | 1 | 1 | 1 | 2 |

| End point values | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 9 | 6 | | |
| Units: Participants | 1 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: QTcF Values Post Baseline by Daily Dose

| End point title | QTcF Values Post Baseline by Daily Dose |
|---|---|

End point description:

Frequency of QT interval prolongation by daily dose (corrected using Fridericia's method, QTcF). To evaluate the effects of rociletinib on the QT (interval from Q wave to T wave)/QTc (interval corrected for

heart rate) interval, all patients underwent serial ECG monitoring at Baseline, on Cycle 1 Day 1, Cycle 1 Day 15, on Day 1 of all subsequent cycles, at the EOT Visit, and as clinically indicated. Worst post-baseline QTcF value was used to categorize each patient. Analysis Population Description - Safety population by daily dose.

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

End point timeframe:

Screening to End of Treatment, up to approximately 42 months

| **End point values** | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 19 | 209 | 245 |
| Units: Participants | | | | |
| QTcF Post-Baseline <450 msec | 34 | 10 | 93 | 99 |
| QTcF Post-Baseline 450-480 msec | 4 | 7 | 71 | 93 |
| QTcF Post-Baseline 481-500 msec | 0 | 1 | 23 | 24 |
| QTcF Post-Baseline >=501 msec | 0 | 1 | 22 | 29 |

| **End point values** | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 6 | | |
| Units: Participants | | | | |
| QTcF Post-Baseline <450 msec | 35 | 2 | | |
| QTcF Post-Baseline 450-480 msec | 30 | 2 | | |
| QTcF Post-Baseline 481-500 msec | 11 | 2 | | |
| QTcF Post-Baseline >=501 msec | 19 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: QtcF Value Change From Baseline

| End point title | QtcF Value Change From Baseline |
|---|---|

End point description:

QTcF value change from baseline by daily dose (corrected using Fridericia's method, QTcF). To evaluate the effects of rociletinib on the QT (interval from Q wave to T wave)/QTc (interval corrected for heart rate) interval, all patients underwent serial ECG monitoring at Baseline, on Cycle 1 Day 1, Cycle 1 Day 15, on Day 1 of all subsequent cycles, at the EOT Visit, and as clinically indicated. Worst post-baseline QTcF value was used to categorize each patient. Analysis Population Description - Safety population by daily dose.

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

End point timeframe:

Screening to End of Treatment, up to approximately 42 months

| End point values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 38 | 19 | 209 | 245 |
| Units: Participants | | | | |
| QTcF Change from Baseline <=30 msec | 29 | 11 | 47 | 55 |
| QTcF Change from Baseline 30-60 msec | 9 | 8 | 104 | 101 |
| QTcF Change from Baseline >60 msec | 0 | 0 | 58 | 89 |

| End point values | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 6 | | |
| Units: Participants | | | | |
| QTcF Change from Baseline <=30 msec | 12 | 1 | | |
| QTcF Change from Baseline 30-60 msec | 39 | 3 | | |
| QTcF Change from Baseline >60 msec | 44 | 2 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS) Determined by Investigator Assessment

| End point title | Overall Survival (OS) Determined by Investigator Assessment |
|---|---|

End point description:

Overall survival was calculated as 1+ the number of days from the first dose of study drug to death due to any cause. Patients without a documented date of death were censored on the date the patient was last known to be alive. Please note: The upper CI limit for the 900 mg BID, 500 mg BID, and 1000 mg BID treatment groups was NA and was replaced with the maximum. Those numbers are 35, 43, and 19 months, respectively.

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

End point timeframe:

Cycle 1 Day 1 to date of death, assessed up to 42 months

| End point values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 9 | 187 | 175 |
| Units: months | | | | |
| median (confidence interval 95%) | 16.3 (6.3 to 17.9) | 23.7 (1.4 to 35) | 18.5 (13.0 to 43) | 15.0 (12.5 to 17.3) |

| End point values | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 4 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.9 (9.9 to 17.7) | 7.2 (2.2 to 19) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS)

| End point title | Progression Free Survival (PFS) According to RECIST Version 1.1 as Determined by Investigator Review (invPFS) |
|---|---|

End point description:

Progression-free survival was calculated as the number of days from the date of the first dose of study drug to the date of disease progression or death due to any cause + 1. Patients without a documented event of disease progression were censored on the date of their last adequate tumor assessment (i.e., radiologic assessment) or date of first dose of study drug if no tumor assessments have been performed. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

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

End point timeframe:

Cycle 1 Day 1 to End of Treatment, up to approximately 42 months

| End point values | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 9 | 187 | 175 |
| Units: months | | | | |
| median (confidence interval 95%) | 2.6 (1.3 to 4.0) | 10.4 (1.4 to 12.2) | 5.7 (4.1 to 6.2) | 5.2 (4.1 to 6.2) |

| End point values | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 4 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.3 (2.9 to 6.1) | 7.2 (2.2 to 16.7) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK Profile of Rociletinib - Cmax

| End point title | PK Profile of Rociletinib - Cmax[16] |
|---|---|

End point description:

Cmax = maximum concentration following administration of rociletinib. Analysis Population Description: PK parameters were assessed in a subset of patients treated with rociletinib. For some parameters, the number analyzed at Day 1 and Day 15 differs from the overall number analyzed based on the number of evaluable samples collected at each time point.

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

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results from the <900 mg BID FB capsule treatment arm are broken down and reported by more specific treatment arm: 150 mg QD FB, 200 mg QD FB, 300 mg QD FB, 450 mg QD FB, 600 mg QD FB, 900 mg QD FB, 100 mg BID FB, 300 mg BID FB, 600 mg BID FB, 400 mg TID FB Capsule.

| End point values | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 19 | 18[17] | 21[18] | 23[19] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 Cmax | 1650 (± 809) | 2800 (± 2128) | 2980 (± 2235) | 2570 (± 1850) |
| Day 15 Cmax | 1510 (± 997) | 2330 (± 1375) | 3070 (± 2272) | 2100 (± 1029) |

Notes:

[17] - Day 1 number analyzed = 18; Day 15 number analyzed = 16

[18] - Day 1 number analyzed = 21; Day 15 number analyzed = 16

[19] - Day 1 number analyzed = 23; Day 15 number analyzed = 22

| End point values | Rociletinib 1000 mg BID HBr Tablets | Rociletinib 150 mg QD FB Capsules | Rociletinib 200 mg QD FB Capsules | Rociletinib 300 mg QD FB Capsules |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6[20] | 9[21] | 3 | 3 |

| | | | | |
|---|---|---|---|---|
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 Cmax | 4250 (± 2678) | 537 (± 71) | 533 (± 63) | 1290 (± 1019) |
| Day 15 Cmax | 2510 (± 728) | 250 (± 188) | 503 (± 377) | 1760 (± 1056) |

Notes:

[20] - Day 1 number analyzed = 6; Day 15 number analyzed = 5

[21] - Day 1 number analyzed = 9; Day 15 number analyzed = 8

| **End point values** | Rociletinib 450 mg QD FB Capsules | Rociletinib 600 mg QD FB Capsules | Rociletinib 900 mg QD FB Capsules | Rociletinib 100 mg BID FB Capsules |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 Cmax | 1800 (± 1224) | 969 (± 824) | 2470 (± 1482) | 574 (± 293) |
| Day 15 Cmax | 942 (± 857) | 981 (± 343) | 2200 (± 1100) | 729 (± 576) |

| **End point values** | Rociletinib 300 mg BID FB Capsules | Rociletinib 600 mg BID FB Capsules | Rociletinib 400 mg TID FB Capsules | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 5 | 3 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 Cmax | 706 (± 88) | 1680 (± 1126) | 704 (± 352) | |
| Day 15 Cmax | 647 (± 304) | 928 (± 95) | 1140 (± 274) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: PK Profile of Rociletinib - Tmax

| End point title | PK Profile of Rociletinib - Tmax[22] |
|---|---|

End point description:

Tmax = time to maximum concentration following administration of rociletinib. Analysis Population Description: PK parameters were assessed in a subset of patients treated with rociletinib. For some parameters, the number analyzed at Day 1 and Day 15 differs from the overall number analyzed based on the number of evaluable samples collected at each time point.

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

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results from the <900 mg BID FB capsule treatment arm are broken down and reported by more specific treatment arm: 150 mg QD FB, 200 mg QD FB, 300 mg QD FB, 450 mg QD FB, 600 mg QD FB, 900 mg QD FB, 100 mg BID FB, 300 mg BID FB, 600 mg BID FB, 400 mg TID FB Capsule.

| End point values | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 19 | 18[23] | 21[24] | 23[25] |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 4 (1 to 8) | 1.5 (.5 to 10) | 2.5 (1 to 8) | 2.5 (1 to 8) |
| Day 15 Tmax | 4 (0 to 8) | 2.5 (1 to 8) | 2.5 (1 to 6) | 2.5 (1 to 8) |

Notes:

[23] - Day 1 number analyzed = 18; Day 15 number analyzed = 16

[24] - Day 1 number analyzed = 21; Day 15 number analyzed = 16

[25] - Day 1 number analyzed = 23; Day 15 number analyzed = 22

| End point values | Rociletinib 1000 mg BID HBr Tablets | Rociletinib 150 mg QD FB Capsules | Rociletinib 200 mg QD FB Capsules | Rociletinib 300 mg QD FB Capsules |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6[26] | 9[27] | 3 | 3 |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 3.25 (1 to 4) | 1.5 (1 to 2.5) | 2.5 (1 to 2.5) | 2.5 (1.5 to 6) |
| Day 15 Tmax | 1.5 (1 to 4) | 2 (1 to 4) | 1.5 (1.5 to 2.5) | 2.5 (2.5 to 4) |

Notes:

[26] - Day 1 number analyzed = 6; Day 15 number analyzed = 5

[27] - Day 1 number analyzed = 9; Day 15 number analyzed = 8

| End point values | Rociletinib 450 mg QD FB Capsules | Rociletinib 600 mg QD FB Capsules | Rociletinib 900 mg QD FB Capsules | Rociletinib 100 mg BID FB Capsules |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 1.5 (1.5 to 2.5) | 2 (1.5 to 2.5) | 2.5 (2.5 to 4) | 2.5 (2.5 to 4) |
| Day 15 Tmax | 1.5 (1.5 to 2.5) | 2.5 (1.5 to 6) | 4 (1.5 to 4) | 2.5 (1.5 to 2.5) |

| End point values | Rociletinib 300 mg BID FB Capsules | Rociletinib 600 mg BID FB Capsules | Rociletinib 400 mg TID FB Capsules | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 3 | 5 | 3 | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 Tmax | 4 (4 to 8) | 4 (2.5 to 6) | 2.5 (1 to 10) | |
| Day 15 Tmax | 1.5 (1 to 6) | 2.5 (2.5 to 4) | 10 (10 to 10) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK Profile of Rociletinib - AUC 0-24

| End point title | PK Profile of Rociletinib - AUC 0-24[28] |
|---|---|

End point description:

AUC 0-24 = area under the curve from 0 to 24 hours. Analysis Population Description: PK parameters were assessed in a subset of patients treated with rociletinib. For some parameters, the number analyzed at Day 1 and Day 15 differs from the overall number analyzed based on the number of evaluable samples collected at each time point. AUC was not calculated for patients in the 400 mg TID treatment group.

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

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results from the <900 mg BID FB capsule treatment arm are broken down and reported by more specific treatment arm: 150 mg QD FB, 200 mg QD FB, 300 mg QD FB, 450 mg QD FB, 600 mg QD FB, 900 mg QD FB, 100 mg BID FB, 300 mg BID FB, 600 mg BID FB.

| End point values | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18[29] | 16[30] | 20[31] | 19[32] |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 AUC 0-24 | 16000 (± 8960) | 26800 (± 13668) | 33100 (± 26149) | 30300 (± 16968) |
| Day 15 AUC 0-24 | 17500 (± 10675) | 23700 (± 13035) | 31700 (± 18386) | 25800 (± 14190) |

Notes:

[29] - Day 1 number analyzed = 18; Day 15 number analyzed = 17

[30] - Day 1 number analyzed = 16; Day 15 number analyzed = 15

[31] - Day 1 number analyzed = 20; Day 15 number analyzed = 15

[32] - Day 1 number analyzed = 19; Day 15 number analyzed = 20

| End point values | Rociletinib 1000 mg BID HBr Tablets | Rociletinib 150 mg QD FB Capsules | Rociletinib 200 mg QD FB Capsules | Rociletinib 300 mg QD FB Capsules |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6 | 9[33] | 2 | 3 |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 AUC 0-24 | 50100 (± 35070) | 2900 (± 290) | 5330 (± 5880) | 8370 (± 6612) |
| Day 15 AUC 0-24 | 28200 (± 16638) | 1540 (± 970) | 3510 (± 2620) | 12100 (± 11616) |

Notes:

[33] - Day 1 number analyzed = 9; Day 15 number analyzed = 8

| End point values | Rociletinib 450 mg QD FB Capsules | Rociletinib 600 mg QD FB Capsules | Rociletinib 900 mg QD FB Capsules | Rociletinib 100 mg BID FB Capsules |
|---|---|---|---|---|

| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
|---|---|---|---|---|
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 AUC 0-24 | 8850 (± 6461) | 5840 (± 3387) | 13300 (± 6650) | 5740 (± 2927) |
| Day 15 AUC 0-24 | 4490 (± 3817) | 4800 (± 2256) | 11500 (± 6555) | 7100 (± 4189) |

| **End point values** | Rociletinib 300 mg BID FB Capsules | Rociletinib 600 mg BID FB Capsules | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 3 | 5 | | |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 AUC 0-24 | 8470 (± 1008) | 20400 (± 12444) | | |
| Day 15 AUC 0-24 | 6080 (± 4560) | 12100 (± 1404) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK Profile of Rociletinib - T 1/2

| End point title | PK Profile of Rociletinib - T 1/2[34] |
|---|---|

End point description:

T 1/2 = elimination half-life following administration of rociletinib. Analysis Population Description: PK parameters were assessed in a subset of patients treated with rociletinib. For some parameters, the number analyzed at Day 1 and Day 15 differs from the overall number analyzed based on the number of evaluable samples collected at each time point. Elimination half-life was not calculated for patients in the 400 mg TID treatment group.

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

End point timeframe:

Cycle 1 Day 1 to Cycle 1 Day 15, or approximately 15 days

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results from the <900 mg BID FB capsule treatment arm are broken down and reported by more specific treatment arm: 150 mg QD FB, 200 mg QD FB, 300 mg QD FB, 450 mg QD FB, 600 mg QD FB, 900 mg QD FB, 100 mg BID FB, 300 mg BID FB, 600 mg BID FB.

| **End point values** | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 15[35] | 14[36] | 18[37] |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 T 1/2 | 2.8 (± .7) | 2.7 (± .7) | 3.5 (± 1.5) | 3.1 (± 1.5) |

| | | | | |
|---|---|---|---|---|
| Day 15 T 1/2 | 2.7 (± 1.9) | 3 (± 1.6) | 3.2 (± .8) | 3.6 (± 3.1) |

Notes:

[35] - Day 1 number analyzed = 15; Day 15 number analyzed = 14

[36] - Day 1 number analyzed = 14; Day 15 number analyzed = 13

[37] - Day 1 number analyzed = 18; Day 15 number analyzed = 19

| **End point values** | Rociletinib 1000 mg BID HBr Tablets | Rociletinib 150 mg QD FB Capsules | Rociletinib 200 mg QD FB Capsules | Rociletinib 300 mg QD FB Capsules |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 6[38] | 9[39] | 2 | 3 |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 T 1/2 | 3.4 (± .9) | 4.8 (± 3.6) | 3.9 (± 2.3) | 4.6 (± 1.7) |
| Day 15 T 1/2 | 3.9 (± 1.9) | 5.5 (± 3.1) | 3.5 (± 1.3) | 4.3 (± 1.2) |

Notes:

[38] - Day 1 number analyzed = 6; Day 15 number analyzed = 5

[39] - Day 1 number analyzed = 9; Day 15 number analyzed = 8

| **End point values** | Rociletinib 450 mg QD FB Capsules | Rociletinib 600 mg QD FB Capsules | Rociletinib 900 mg QD FB Capsules | Rociletinib 100 mg BID FB Capsules |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 3 | 3 | 3 | 3 |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 T 1/2 | 3.7 (± 1.1) | 4.4 (± .9) | 3.5 (± 2.8) | 3 (± .8) |
| Day 15 T 1/2 | 3.9 (± 2.5) | 4.1 (± 2.2) | 3.5 (± .56) | 3.1 (± .9) |

| **End point values** | Rociletinib 300 mg BID FB Capsules | Rociletinib 600 mg BID FB Capsules | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2 | 4[40] | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 T 1/2 | 3.5 (± 1) | 3.6 (± .9) | | |
| Day 15 T 1/2 | 2.9 (± .7) | 4.7 (± 3.4) | | |

Notes:

[40] - Day 1 number analyzed = 4; Day 15 number analyzed = 5

## Statistical analyses

No statistical analyses for this end point

## Secondary: Food Effect on PK of Rociletinib - Cmax

| End point title | Food Effect on PK of Rociletinib - Cmax |
|---|---|

End point description:

Cmax = maximum concentration following administration of rociletinib. The effect of food on rociletinib PK parameters was assessed over a 24-hour period in blood samples from a subset of 3 patients. These patients were given a single dose of rociletinib 150mg FB 1 week prior (Day -7) to the start of

continuous daily dosing after fasting. On Day 1 of Cycle 1, patients consumed a high-fat, high-calorie breakfast at the study site prior to receiving rociletinib. On each day, patients underwent blood sampling for PK at the specified time points.

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

End point timeframe:

Day -7 prior to Cycle 1 Day 1, or approximately 7 days

| **End point values** | Rociletinib 150 mg QD FB Capsules | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cmax Fasting | 727 (± 354) | | | |
| Cmax Fed | 1873 (± 2570) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Food Effect on PK of Rociletinib - Tmax

| End point title | Food Effect on PK of Rociletinib - Tmax |
|---|---|

End point description:

Tmax = time to maximum concentration following administration of rociletinib. The effect of food on rociletinib PK parameters was assessed over a 24-hour period in blood samples from a subset of 3 patients. These patients were given a single dose of rociletinib 150mg FB 1 week prior (Day -7) to the start of continuous daily dosing after fasting. On Day 1 of Cycle 1, patients consumed a high-fat, high-calorie breakfast at the study site prior to receiving rociletinib. On each day, patients underwent blood sampling for PK at the specified time points.

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

End point timeframe:

Day -7 prior to Cycle 1 Day 1, or approximately 7 days

| **End point values** | Rociletinib 150 mg QD FB Capsules | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 | | | |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Tmax Fasting | 1.5 (1 to 2.5) | | | |
| Tmax Fed | 4.8 (2.5 to 8) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Food Effect on PK of Rociletinib - AUC 0-24

| End point title | Food Effect on PK of Rociletinib - AUC 0-24 |
|---|---|

End point description:

AUC 0-24 = area under the curve from 0 to 24 hours. The effect of food on rociletinib PK parameters was assessed over a 24-hour period in blood samples from a subset of 3 patients. These patients were given a single dose of rociletinib 150mg FB 1 week prior (Day -7) to the start of continuous daily dosing after fasting. On Day 1 of Cycle 1, patients consumed a high-fat, high-calorie breakfast at the study site prior to receiving rociletinib. On each day, patients underwent blood sampling for PK at the specified time points.

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

End point timeframe:

Day -7 prior to Cycle 1 Day 1, or approximately 7 days

| **End point values** | Rociletinib 150 mg QD FB Capsules | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3[41] | | | |
| Units: ng*hr/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC 0-24 Fasting | 4780 (± 3625) | | | |
| AUC 0-24 Fed | 4455 (± 2256) | | | |

Notes:

[41] - Fasting number analyzed = 3; Fed number analyzed = 2

### Statistical analyses

No statistical analyses for this end point

### Secondary: Food Effect on PK of Rociletinib - C24

| End point title | Food Effect on PK of Rociletinib - C24 |
|---|---|

End point description:

C24 = rociletinib plasma concentration at 24 hours post the morning dose. The effect of food on rociletinib PK parameters was assessed over a 24-hour period in blood samples from a subset of 3 patients. These patients were given a single dose of rociletinib 150mg FB 1 week prior (Day -7) to the start of continuous daily dosing after fasting. On Day 1 of Cycle 1, patients consumed a high-fat, high-calorie breakfast at the study site prior to receiving rociletinib. On each day, patients underwent blood sampling for PK at the specified time points.

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

End point timeframe:

Day -7 prior to Cycle 1 Day 1, or approximately 7 days

| End point values | Rociletinib 150 mg QD FB Capsules | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| C24 Fasting | 21.3 (± 22) | | | |
| C24 Fed | 46.5 (± 51) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Food Effect on PK of Rociletinib - T 1/2

| End point title | Food Effect on PK of Rociletinib - T 1/2 |
|---|---|

End point description:

T 1/2 = elimination half-life following administration of rociletinib. The effect of food on rociletinib PK parameters was assessed over a 24-hour period in blood samples from a subset of 3 patients. These patients were given a single dose of rociletinib 150mg FB 1 week prior (Day -7) to the start of continuous daily dosing after fasting. On Day 1 of Cycle 1, patients consumed a high-fat, high-calorie breakfast at the study site prior to receiving rociletinib. On each day, patients underwent blood sampling for PK at the specified time points. Please note: Since N=1, the standard deviation for the T 1/2 Fed category can not be calculated. Thus "999" is entered as a placeholder.

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

End point timeframe:

Day -7 prior to Cycle 1 Day 1, or approximately 7 days

| End point values | Rociletinib 150 mg QD FB Capsules | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3[42] | | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| T 1/2 Fasting | 4.3 (± 1) | | | |
| T 1/2 Fed | 3.1 (± 999) | | | |

Notes:

[42] - Fasting number analyzed = 3; Fed number analyzed = 1

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of first dose of study drug and within 28 days after last dose of study drug, or approximately 9 months.

Adverse event reporting additional description:

In addition, study procedure-related AEs that occur after signing of the informed consent form and before first dose of study drug were expected to be reported. Any Serious Adverse Events or Adverse Events of Special Interest were followed until resolution or stabilization, or until patient is lost to follow-up.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Rociletinib <900 mg BID FB Capsules |

Reporting group description:

Rociletinib free base (FB) dose <900 mg twice a day (BID). FB doses tested ranged from 150 mg once a day (QD) up to 900 mg twice a day (BID).

| | |
|---|---|
| Reporting group title | Rociletinib 900 mg BID FB Capsules |

Reporting group description:

Rociletinib free base (FB) dose 900 mg twice a day (BID)

| | |
|---|---|
| Reporting group title | Rociletinib 500 mg BID HBr Tablets |

Reporting group description:

Rociletinib hydrobromide (HBr) dose 500 mg twice a day (BID)

| | |
|---|---|
| Reporting group title | Rociletinib 625 mg BID HBr Tablets |

Reporting group description:

Rociletinib hydrobromide (HR) dose 625 mg twice a day (BID)

| | |
|---|---|
| Reporting group title | Rociletinib 750 mg BID HBr Tablets |

Reporting group description:

Rociletinib hydrobromide (HBr) dose 750 mg twice a day (BID)

| | |
|---|---|
| Reporting group title | Rociletinib 1000 mg BID HBr Tablets |

Reporting group description:

Rociletinib hydrobromide (HBr) dose 1000 mg twice a day (BID)

| Serious adverse events | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 38 (36.84%) | 8 / 19 (42.11%) | 106 / 209 (50.72%) |
| number of deaths (all causes) | 4 | 4 | 31 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 5 / 19 (26.32%) | 25 / 209 (11.96%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 5 | 0 / 28 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | 0 / 23 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to skin | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subgaleal haematoma | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 4 / 209 (1.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cough | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 8 / 209 (3.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 3 / 209 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Basilar artery thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 3 / 209 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord oedema | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 4 / 209 (1.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Ear and labyrinth disorders** | | | |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal dilatation | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 5 / 209 (2.39%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 5 / 209 (2.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 5 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 7 / 209 (3.35%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 3 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver injury | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 7 / 209 (3.35%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 2 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 4 / 209 (1.91%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Serratia bacteraemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 3 / 209 (1.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 4 / 209 (1.91%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 21 / 209 (10.05%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 22 / 23 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 5 / 209 (2.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 138 / 245 (56.33%) | 54 / 95 (56.84%) | 5 / 6 (83.33%) |
| number of deaths (all causes) | 40 | 19 | 3 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 37 / 245 (15.10%) | 21 / 95 (22.11%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 38 | 0 / 22 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 34 | 0 / 17 | 0 / 1 |

| | | | |
|---|---|---|---|
| Malignant pleural effusion | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to skin | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subgaleal haematoma | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **General disorders and administration site conditions** | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Sudden death | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 245 (4.08%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 245 (2.04%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hallucination | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaw fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Nervous system disorders** | | | |
| Basilar artery thrombosis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Ear and labyrinth disorders** | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Eye disorders** | | | |
| Cataract | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 3 / 95 (3.16%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 6 / 6 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 3 / 7 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal dilatation | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mallory-Weiss syndrome | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 245 (1.63%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 3 / 7 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Chondrocalcinosis pyrophosphate | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic infection | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 10 / 245 (4.08%) | 7 / 95 (7.37%) | 2 / 6 (33.33%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 8 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia influenzal | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Serratia bacteraemia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 7 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 19 / 245 (7.76%) | 7 / 95 (7.37%) | 2 / 6 (33.33%) |
| occurrences causally related to treatment / all | 21 / 21 | 9 / 9 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 245 (1.63%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Rociletinib <900 mg BID FB Capsules | Rociletinib 900 mg BID FB Capsules | Rociletinib 500 mg BID HBr Tablets |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 38 (97.37%) | 19 / 19 (100.00%) | 208 / 209 (99.52%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 11 / 38 (28.95%) | 5 / 19 (26.32%) | 28 / 209 (13.40%) |
| occurrences (all) | 11 | 8 | 32 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 0 / 19 (0.00%) | 16 / 209 (7.66%) |
| occurrences (all) | 5 | 0 | 34 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 0 | 1 | 4 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 1 / 19 (5.26%) | 28 / 209 (13.40%) |
| occurrences (all) | 8 | 2 | 53 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| Chills | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 1 | 1 | 6 |
| Face oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 8 / 19 (42.11%) | 109 / 209 (52.15%) |
| occurrences (all) | 12 | 9 | 160 |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Feeling cold | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 1 | 0 | 2 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 19 (15.79%) | 8 / 209 (3.83%) |
| occurrences (all) | 0 | 4 | 9 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 1 | 1 | 6 |
| Malaise | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 1 | 5 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 1 / 19 (5.26%) | 9 / 209 (4.31%) |
| occurrences (all) | 3 | 1 | 10 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 19 (5.26%) | 40 / 209 (19.14%) |
| occurrences (all) | 4 | 3 | 48 |
| Pain | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 7 / 209 (3.35%) |
| occurrences (all) | 1 | 1 | 7 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 19 (10.53%) | 19 / 209 (9.09%) |
| occurrences (all) | 5 | 2 | 27 |
| Temperature intolerance | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Immune system disorders | | | |

| | | | |
|---|---|---|---|
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 2 | 0 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 3 / 19 (15.79%) | 62 / 209 (29.67%) |
| occurrences (all) | 9 | 3 | 79 |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 2 | 1 | 4 |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | 2 / 19 (10.53%) | 51 / 209 (24.40%) |
| occurrences (all) | 11 | 2 | 77 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 19 (0.00%) | 12 / 209 (5.74%) |
| occurrences (all) | 3 | 0 | 16 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 19 (10.53%) | 7 / 209 (3.35%) |
| occurrences (all) | 2 | 2 | 10 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 1 | 1 | 3 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 6 / 209 (2.87%) |
| occurrences (all) | 0 | 2 | 6 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 1 | 1 | 6 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 8 / 209 (3.83%) |
| occurrences (all) | 2 | 0 | 8 |
| Paranasal sinus hypersecretion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences (all) | 2 | 0 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 19 (10.53%) | 6 / 209 (2.87%) |
| occurrences (all) | 2 | 2 | 7 |
| Pleuritic pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 19 (10.53%) | 1 / 209 (0.48%) |
| occurrences (all) | 3 | 2 | 1 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 1 | 1 | 3 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 1 | 6 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Throat tightness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 1 | 1 | 5 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 19 / 209 (9.09%) |
| occurrences (all) | 0 | 2 | 19 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 8 / 209 (3.83%) |
| occurrences (all) | 0 | 0 | 8 |

| | | | |
|---|---|---|---|
| Depression | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 19 (15.79%) | 8 / 209 (3.83%) |
| occurrences (all) | 3 | 3 | 8 |
| Insomnia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 19 (10.53%) | 19 / 209 (9.09%) |
| occurrences (all) | 4 | 2 | 21 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 19 (15.79%) | 19 / 209 (9.09%) |
| occurrences (all) | 3 | 4 | 25 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 19 (21.05%) | 21 / 209 (10.05%) |
| occurrences (all) | 4 | 5 | 38 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 19 (5.26%) | 13 / 209 (6.22%) |
| occurrences (all) | 5 | 1 | 21 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 4 / 19 (21.05%) | 16 / 209 (7.66%) |
| occurrences (all) | 0 | 11 | 34 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 13 / 209 (6.22%) |
| occurrences (all) | 0 | 4 | 19 |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 1 | 1 | 5 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Electrocardiogram QT prolonged | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 19 (15.79%) | 61 / 209 (29.19%) |
| occurrences (all) | 0 | 5 | 135 |
| Electrocardiogram T wave abnormal | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Insulin C-peptide increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 0 | 6 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 12 / 209 (5.74%) |
| occurrences (all) | 0 | 0 | 23 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 3 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 20 / 209 (9.57%) |
| occurrences (all) | 0 | 0 | 30 |
| QRS axis abnormal | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 2 | 7 |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 19 (21.05%) | 59 / 209 (28.23%) |
| occurrences (all) | 6 | 6 | 69 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 19 / 209 (9.09%) |
| occurrences (all) | 1 | 0 | 43 |
| Injury, poisoning and procedural | | | |

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|---|---|---|---|
| complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 3 / 19 (15.79%) | 14 / 209 (6.70%) |
| occurrences (all) | 0 | 3 | 14 |
| Fall | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 9 / 209 (4.31%) |
| occurrences (all) | 0 | 2 | 10 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 10 / 209 (4.78%) |
| occurrences (all) | 1 | 1 | 12 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Amnesia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 1 | 1 | 4 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 0 | 1 |
| Disturbance in attention | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 4 / 19 (21.05%) | 25 / 209 (11.96%) |
| occurrences (all) | 4 | 4 | 32 |
| Dysarthria | | | |

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| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 19 (10.53%) | 17 / 209 (8.13%) |
| occurrences (all) | 1 | 2 | 18 |
| Headache | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 5 / 19 (26.32%) | 57 / 209 (27.27%) |
| occurrences (all) | 7 | 6 | 72 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 1 | 3 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 3 / 19 (15.79%) | 5 / 209 (2.39%) |
| occurrences (all) | 1 | 3 | 6 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 1 | 1 | 6 |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 10 / 209 (4.78%) |
| occurrences (all) | 3 | 0 | 10 |
| Restless legs syndrome | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 0 | 1 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 3 / 19 (15.79%) | 7 / 209 (3.35%) |
| occurrences (all) | 1 | 3 | 7 |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |

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|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 3 / 19 (15.79%) | 47 / 209 (22.49%) |
| occurrences (all) | 5 | 5 | 91 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 2 | 1 |
| Leukocytosis | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 3 / 209 (1.44%) |
| occurrences (all) | 2 | 0 | 3 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 8 / 209 (3.83%) |
| occurrences (all) | 1 | 0 | 9 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 9 / 209 (4.31%) |
| occurrences (all) | 0 | 1 | 14 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 19 (0.00%) | 10 / 209 (4.78%) |
| occurrences (all) | 2 | 0 | 15 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 3 / 19 (15.79%) | 21 / 209 (10.05%) |
| occurrences (all) | 3 | 8 | 33 |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysacusis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 16 / 209 (7.66%) |
| occurrences (all) | 0 | 0 | 21 |
| Diplopia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Dry eye | | | |

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| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 1 | 1 | 4 |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 13 / 209 (6.22%) |
| occurrences (all) | 1 | 1 | 13 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 4 / 209 (1.91%) |
| occurrences (all) | 1 | 1 | 4 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 0 | 5 |
| Vitreous floaters | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 1 | 3 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 8 / 209 (3.83%) |
| occurrences (all) | 0 | 1 | 8 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 4 / 19 (21.05%) | 25 / 209 (11.96%) |
| occurrences (all) | 4 | 4 | 38 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 15 / 209 (7.18%) |
| occurrences (all) | 2 | 0 | 15 |
| Constipation | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 2 / 19 (10.53%) | 42 / 209 (20.10%) |
| occurrences (all) | 11 | 2 | 56 |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 11 / 19 (57.89%) | 121 / 209 (57.89%) |
| occurrences (all) | 14 | 14 | 193 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 26 / 209 (12.44%) |
| occurrences (all) | 3 | 0 | 35 |

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| Dyspepsia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 19 (10.53%) | 7 / 209 (3.35%) |
| occurrences (all) | 3 | 2 | 7 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 1 | 3 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 22 / 209 (10.53%) |
| occurrences (all) | 0 | 4 | 25 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Ileus | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 2 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences (all) | 3 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 14 / 38 (36.84%) | 11 / 19 (57.89%) | 95 / 209 (45.45%) |
| occurrences (all) | 23 | 18 | 143 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 0 | 9 |
| Retching | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 1 | 3 |
| Toothache | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 1 / 209 (0.48%) |
| occurrences (all) | 2 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 6 / 19 (31.58%) | 65 / 209 (31.10%) |
| occurrences (all) | 16 | 10 | 93 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |

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| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 2 | 1 | 8 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 13 / 209 (6.22%) |
| occurrences (all) | 2 | 0 | 14 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 3 / 19 (15.79%) | 14 / 209 (6.70%) |
| occurrences (all) | 1 | 3 | 17 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 1 | 1 | 5 |
| Rash | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 19 (10.53%) | 17 / 209 (8.13%) |
| occurrences (all) | 3 | 3 | 18 |
| Rash morbilliform | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin erosion | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Micturition urgency | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 8 / 209 (3.83%) |
| occurrences (all) | 1 | 1 | 8 |
| Renal impairment | | | |

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| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urge incontinence | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 3 / 19 (15.79%) | 23 / 209 (11.00%) |
| occurrences (all) | 10 | 4 | 28 |
| Back pain | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 3 / 19 (15.79%) | 26 / 209 (12.44%) |
| occurrences (all) | 8 | 4 | 32 |
| Bone pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 4 / 209 (1.91%) |
| occurrences (all) | 0 | 2 | 4 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 5 / 209 (2.39%) |
| occurrences (all) | 0 | 1 | 5 |
| Joint swelling | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 6 / 19 (31.58%) | 57 / 209 (27.27%) |
| occurrences (all) | 7 | 8 | 74 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 9 / 209 (4.31%) |
| occurrences (all) | 0 | 2 | 10 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 19 (10.53%) | 12 / 209 (5.74%) |
| occurrences (all) | 3 | 4 | 14 |
| Musculoskeletal discomfort | | | |

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| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 3 | 0 | 2 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 1 / 19 (5.26%) | 20 / 209 (9.57%) |
| occurrences (all) | 8 | 1 | 21 |
| Myalgia | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 4 / 19 (21.05%) | 23 / 209 (11.00%) |
| occurrences (all) | 7 | 5 | 33 |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 0 / 19 (0.00%) | 14 / 209 (6.70%) |
| occurrences (all) | 3 | 0 | 17 |
| Infections and infestations | | | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 3 / 209 (1.44%) |
| occurrences (all) | 0 | 1 | 3 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 1 | 1 | 6 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 19 (5.26%) | 12 / 209 (5.74%) |
| occurrences (all) | 3 | 1 | 12 |

| | | | |
|---|---|---|---|
| Rhinitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 2 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 0 | 1 | 6 |
| Tooth infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 2 / 209 (0.96%) |
| occurrences (all) | 0 | 1 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 2 / 19 (10.53%) | 23 / 209 (11.00%) |
| occurrences (all) | 4 | 2 | 26 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 27 / 209 (12.92%) |
| occurrences (all) | 1 | 3 | 39 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 1 / 209 (0.48%) |
| occurrences (all) | 0 | 1 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 9 / 38 (23.68%) | 10 / 19 (52.63%) | 80 / 209 (38.28%) |
| occurrences (all) | 9 | 14 | 114 |
| Dehydration | | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 4 / 19 (21.05%) | 21 / 209 (10.05%) |
| occurrences (all) | 3 | 4 | 24 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 0 | 2 | 6 |
| Gout | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 0 / 209 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 10 / 19 (52.63%) | 113 / 209 (54.07%) |
| occurrences (all) | 7 | 15 | 294 |
| Hyperkalaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 19 (5.26%) | 7 / 209 (3.35%) |
| occurrences (all) | 1 | 1 | 9 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 19 (10.53%) | 18 / 209 (8.61%) |
| occurrences (all) | 3 | 3 | 21 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 6 / 209 (2.87%) |
| occurrences (all) | 0 | 1 | 7 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 19 (0.00%) | 2 / 209 (0.96%) |
| occurrences (all) | 2 | 0 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 19 (5.26%) | 27 / 209 (12.92%) |
| occurrences (all) | 0 | 2 | 34 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 0 / 19 (0.00%) | 25 / 209 (11.96%) |
| occurrences (all) | 0 | 0 | 32 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 2 / 19 (10.53%) | 25 / 209 (11.96%) |
| occurrences (all) | 0 | 2 | 35 |

| **Non-serious adverse events** | Rociletinib 625 mg BID HBr Tablets | Rociletinib 750 mg BID HBr Tablets | Rociletinib 1000 mg BID HBr Tablets |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 244 / 245 (99.59%) | 95 / 95 (100.00%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 38 / 245 (15.51%) | 26 / 95 (27.37%) | 1 / 6 (16.67%) |
| occurrences (all) | 43 | 34 | 1 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 7 / 95 (7.37%) | 0 / 6 (0.00%) |
| occurrences (all) | 20 | 9 | 0 |
| Hypotension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 245 (3.67%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 2 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 34 / 245 (13.88%) | 17 / 95 (17.89%) | 1 / 6 (16.67%) |
| occurrences (all) | 52 | 24 | 1 |
| Catheter site pain | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 3 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 1 | 0 |
| Face oedema | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 124 / 245 (50.61%) | 47 / 95 (49.47%) | 3 / 6 (50.00%) |
| occurrences (all) | 190 | 90 | 6 |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Gait disturbance | | | |
| subjects affected / exposed | 10 / 245 (4.08%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 11 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Malaise | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Non-cardiac chest pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 18 / 245 (7.35%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 24 | 4 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 31 / 245 (12.65%) | 14 / 95 (14.74%) | 0 / 6 (0.00%) |
| occurrences (all) | 35 | 19 | 0 |
| Pain | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 6 / 95 (6.32%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 6 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 245 (11.02%) | 7 / 95 (7.37%) | 0 / 6 (0.00%) |
| occurrences (all) | 36 | 7 | 0 |
| Temperature intolerance | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 59 / 245 (24.08%) | 15 / 95 (15.79%) | 1 / 6 (16.67%) |
| occurrences (all) | 72 | 15 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 2 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 65 / 245 (26.53%) | 20 / 95 (21.05%) | 2 / 6 (33.33%) |
| occurrences (all) | 89 | 29 | 2 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 7 / 95 (7.37%) | 0 / 6 (0.00%) |
| occurrences (all) | 10 | 7 | 0 |
| Epistaxis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 245 (4.90%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 14 | 2 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 17 | 1 | 1 |
| Hypoxia | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 7 | 3 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 2 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 7 | 1 | 0 |
| Paranasal sinus hypersecretion | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 13 / 245 (5.31%) | 5 / 95 (5.26%) | 1 / 6 (16.67%) |
| occurrences (all) | 17 | 7 | 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 3 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 2 / 95 (2.11%) | 1 / 6 (16.67%) |
| occurrences (all) | 8 | 2 | 1 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Throat tightness | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 20 / 245 (8.16%) | 8 / 95 (8.42%) | 1 / 6 (16.67%) |
| occurrences (all) | 23 | 8 | 1 |
| Confusional state | | | |
| subjects affected / exposed | 13 / 245 (5.31%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 15 | 4 | 0 |
| Depression | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 4 / 95 (4.21%) | 1 / 6 (16.67%) |
| occurrences (all) | 12 | 4 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 31 / 245 (12.65%) | 8 / 95 (8.42%) | 0 / 6 (0.00%) |
| occurrences (all) | 33 | 10 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 26 / 245 (10.61%) | 8 / 95 (8.42%) | 0 / 6 (0.00%) |
| occurrences (all) | 48 | 12 | 0 |
| Amylase increased | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 26 / 245 (10.61%) | 10 / 95 (10.53%) | 0 / 6 (0.00%) |
| occurrences (all) | 40 | 11 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 7 / 95 (7.37%) | 1 / 6 (16.67%) |
| occurrences (all) | 25 | 8 | 1 |
| Blood bilirubin increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 245 (6.12%) | 13 / 95 (13.68%) | 1 / 6 (16.67%) |
| occurrences (all) | 24 | 20 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 20 / 245 (8.16%) | 7 / 95 (7.37%) | 1 / 6 (16.67%) |
| occurrences (all) | 38 | 12 | 3 |
| Blood glucose increased | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 7 / 95 (7.37%) | 2 / 6 (33.33%) |
| occurrences (all) | 12 | 15 | 2 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 77 / 245 (31.43%) | 33 / 95 (34.74%) | 3 / 6 (50.00%) |
| occurrences (all) | 185 | 65 | 3 |
| Electrocardiogram T wave abnormal | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 2 / 95 (2.11%) | 1 / 6 (16.67%) |
| occurrences (all) | 12 | 2 | 1 |
| Insulin C-peptide increased | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 11 | 5 | 0 |
| Lipase increased | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 1 | 2 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 17 | 2 | 0 |
| Neutrophil count increased | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Platelet count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 17 / 245 (6.94%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 37 | 6 | 0 |
| QRS axis abnormal | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 4 | 1 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 63 / 245 (25.71%) | 39 / 95 (41.05%) | 2 / 6 (33.33%) |
| occurrences (all) | 87 | 50 | 3 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 20 / 245 (8.16%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 51 | 7 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 14 / 245 (5.71%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 14 | 4 | 0 |
| Fall | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 4 | 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Amnesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 245 (0.82%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Ataxia | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Balance disorder | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 4 | 0 | 1 |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 41 / 245 (16.73%) | 14 / 95 (14.74%) | 1 / 6 (16.67%) |
| occurrences (all) | 50 | 14 | 2 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 18 | 5 | 0 |
| Headache | | | |
| subjects affected / exposed | 57 / 245 (23.27%) | 20 / 95 (21.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 73 | 26 | 1 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 7 | 4 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 9 | 5 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 17 / 245 (6.94%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 18 | 5 | 0 |
| Restless legs syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seizure | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 6 | 6 | 0 |
| Tension headache | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 7 / 245 (2.86%) | 4 / 95 (4.21%) | 1 / 6 (16.67%) |
| occurrences (all) | 8 | 5 | 2 |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 74 / 245 (30.20%) | 19 / 95 (20.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 131 | 41 | 1 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukocytosis | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 6 / 95 (6.32%) | 0 / 6 (0.00%) |
| occurrences (all) | 10 | 6 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 19 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 7 / 95 (7.37%) | 0 / 6 (0.00%) |
| occurrences (all) | 14 | 11 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 19 / 245 (7.76%) | 17 / 95 (17.89%) | 0 / 6 (0.00%) |
| occurrences (all) | 30 | 41 | 0 |

| | | | |
|---|---|---|---|
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysacusis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 29 / 245 (11.84%) | 17 / 95 (17.89%) | 2 / 6 (33.33%) |
| occurrences (all) | 34 | 21 | 3 |
| Diplopia | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry eye | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 18 / 245 (7.35%) | 13 / 95 (13.68%) | 0 / 6 (0.00%) |
| occurrences (all) | 21 | 15 | 0 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 3 / 95 (3.16%) | 1 / 6 (16.67%) |
| occurrences (all) | 5 | 3 | 1 |
| Vitreous floaters | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 4 | 0 |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 39 / 245 (15.92%) | 17 / 95 (17.89%) | 0 / 6 (0.00%) |
| occurrences (all) | 51 | 21 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 18 / 245 (7.35%) | 11 / 95 (11.58%) | 2 / 6 (33.33%) |
| occurrences (all) | 23 | 14 | 2 |
| Constipation | | | |
| subjects affected / exposed | 94 / 245 (38.37%) | 26 / 95 (27.37%) | 2 / 6 (33.33%) |
| occurrences (all) | 117 | 31 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 146 / 245 (59.59%) | 54 / 95 (56.84%) | 3 / 6 (50.00%) |
| occurrences (all) | 292 | 82 | 4 |
| Dry mouth | | | |
| subjects affected / exposed | 22 / 245 (8.98%) | 16 / 95 (16.84%) | 0 / 6 (0.00%) |
| occurrences (all) | 23 | 17 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 5 / 95 (5.26%) | 1 / 6 (16.67%) |
| occurrences (all) | 6 | 5 | 1 |
| Flatulence | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 4 | 2 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 26 / 245 (10.61%) | 12 / 95 (12.63%) | 0 / 6 (0.00%) |
| occurrences (all) | 31 | 14 | 0 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 3 / 245 (1.22%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 138 / 245 (56.33%) | 51 / 95 (53.68%) | 3 / 6 (50.00%) |
| occurrences (all) | 218 | 78 | 6 |
| Pancreatitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 245 (2.04%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 5 | 2 | 2 |
| Retching | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Toothache | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 82 / 245 (33.47%) | 32 / 95 (33.68%) | 2 / 6 (33.33%) |
| occurrences (all) | 135 | 46 | 2 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 12 | 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 11 / 95 (11.58%) | 0 / 6 (0.00%) |
| occurrences (all) | 10 | 15 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 18 / 245 (7.35%) | 5 / 95 (5.26%) | 1 / 6 (16.67%) |
| occurrences (all) | 18 | 5 | 1 |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 4 / 95 (4.21%) | 0 / 6 (0.00%) |
| occurrences (all) | 15 | 4 | 0 |
| Rash | | | |
| subjects affected / exposed | 13 / 245 (5.31%) | 12 / 95 (12.63%) | 0 / 6 (0.00%) |
| occurrences (all) | 18 | 12 | 0 |
| Rash morbilliform | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin erosion | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Micturition urgency | | | |
| subjects affected / exposed | 2 / 245 (0.82%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 17 | 1 | 0 |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urge incontinence | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract disorder | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 31 / 245 (12.65%) | 13 / 95 (13.68%) | 0 / 6 (0.00%) |
| occurrences (all) | 35 | 14 | 0 |
| Back pain | | | |
| subjects affected / exposed | 43 / 245 (17.55%) | 15 / 95 (15.79%) | 0 / 6 (0.00%) |
| occurrences (all) | 48 | 16 | 0 |
| Bone pain | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Joint swelling | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 245 (0.41%) | 3 / 95 (3.16%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 3 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 71 / 245 (28.98%) | 27 / 95 (28.42%) | 2 / 6 (33.33%) |
| occurrences (all) | 111 | 35 | 3 |
| Muscular weakness | | | |
| subjects affected / exposed | 12 / 245 (4.90%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 6 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 21 / 245 (8.57%) | 13 / 95 (13.68%) | 1 / 6 (16.67%) |
| occurrences (all) | 27 | 14 | 1 |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 22 / 245 (8.98%) | 10 / 95 (10.53%) | 0 / 6 (0.00%) |
| occurrences (all) | 23 | 11 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 10 / 95 (10.53%) | 1 / 6 (16.67%) |
| occurrences (all) | 18 | 10 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 23 / 245 (9.39%) | 5 / 95 (5.26%) | 0 / 6 (0.00%) |
| occurrences (all) | 31 | 6 | 0 |
| Infections and infestations | | | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Candida infection | | | |
| subjects affected / exposed | 5 / 245 (2.04%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 4 / 245 (1.63%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 5 | 0 | 1 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Eye infection | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 1 / 95 (1.05%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 0 / 95 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 12 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 15 / 245 (6.12%) | 11 / 95 (11.58%) | 2 / 6 (33.33%) |
| occurrences (all) | 18 | 15 | 3 |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 11 | 1 | 0 |
| Tooth infection | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 1 / 95 (1.05%) | 0 / 6 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 16 / 245 (6.53%) | 14 / 95 (14.74%) | 1 / 6 (16.67%) |
| occurrences (all) | 19 | 14 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 25 / 245 (10.20%) | 18 / 95 (18.95%) | 0 / 6 (0.00%) |
| occurrences (all) | 38 | 28 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 245 (0.41%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 92 / 245 (37.55%) | 43 / 95 (45.26%) | 4 / 6 (66.67%) |
| occurrences (all) | 134 | 59 | 4 |
| Dehydration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 30 / 245 (12.24%) | 12 / 95 (12.63%) | 0 / 6 (0.00%) |
| occurrences (all) | 36 | 16 | 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 9 / 245 (3.67%) | 11 / 95 (11.58%) | 0 / 6 (0.00%) |
| occurrences (all) | 11 | 16 | 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 245 (0.00%) | 0 / 95 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 147 / 245 (60.00%) | 56 / 95 (58.95%) | 3 / 6 (50.00%) |
| occurrences (all) | 431 | 134 | 6 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 6 / 245 (2.45%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 7 | 3 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 22 / 245 (8.98%) | 3 / 95 (3.16%) | 0 / 6 (0.00%) |
| occurrences (all) | 31 | 9 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 11 / 245 (4.49%) | 2 / 95 (2.11%) | 0 / 6 (0.00%) |
| occurrences (all) | 14 | 3 | 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 8 / 245 (3.27%) | 6 / 95 (6.32%) | 0 / 6 (0.00%) |
| occurrences (all) | 8 | 7 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 44 / 245 (17.96%) | 14 / 95 (14.74%) | 1 / 6 (16.67%) |
| occurrences (all) | 58 | 16 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 30 / 245 (12.24%) | 10 / 95 (10.53%) | 2 / 6 (33.33%) |
| occurrences (all) | 40 | 13 | 2 |
| Hyponatraemia | | | |
| subjects affected / exposed | 24 / 245 (9.80%) | 8 / 95 (8.42%) | 1 / 6 (16.67%) |
| occurrences (all) | 28 | 14 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 January 2012 | Patient enrollment began into the Phase 1 portion of the study. Dose escalation was initiated at 150 mg QD with the FB rociletinib formulation. |
| 04 October 2012 | Patients were enrolled at approximately 6 sites for Phase 1 and approximately 12 to 15 sites for Phase 2. |
| 08 July 2013 | The rociletinib 125 mg HBr tablet was introduced under this amendment and a CRM replaced the 3 + 3 dose escalation schema. Enrollment was increased to approximately 170 patients in both phases at up to 8 investigative sites for Phase 1 and 12 to 15 for Phase 2. An additional Phase 2 cohort was added, and Cohorts A and B were defined. |
| 10 December 2013 | A higher strength 250 mg rociletinib HBr tablet was made available in addition to the 125 mg strength in the previous amendment. An initial RP2D of 750 mg BID was selected for Phase 2 and enrollment into Phase 2 was initiated under this amendment (starting in January 2014). Inclusion and exclusion criteria were modified, and minor adjustments were made to the sample size and number of study sites and regions to reflect the current status of the study (up to 22 investigative sites for Phase 2). Fasting glucose and hemoglobin A1c were added as clinical laboratory investigation, and guidance for management of rociletinib-related hyperglycemia was provided. |
| 17 April 2014 | The total number of patients increased from 172 to approximately 600 (Phase 1: N≈110; Phase 2: N≈490). The number of investigative sites for Phase 2 was increased to approximately 50 sites to accommodate the increase in patient number. The study now had 80% power to detect a 20% difference in ORR between 2 dose groups at the 10% significance level. Formal safety data reviews were performed following the enrollment of every 50 patients, and no less frequently than every quarter. For Phase 2, the primary endpoints of ORR and DOR were specified to be assessed by the investigator, and additional secondary endpoints of OS and DCR were added. Cohort C was added to Phase 2, and rociletinib HBr tablet dose levels of 500 mg BID and 625 mg BID were added to Cohorts A and B in order to evaluate dose response and tolerability in more detail. Patients were no longer to be enrolled at a starting dose of 750 mg BID. Guidelines for management of QT prolongation and hyperglycemia were updated based on identification of these events as key safety signals following completion of the dose escalation portion of Phase 1 in January 2014. |
| 07 August 2014 | This amendment allowed the sponsor to enroll the RP2D of 625 mg BID before the 500 mg BID dose in order to increase experience with the RP2D to support the ongoing Phase 2 and Phase 3 rociletinib programs and to increase the total number of patients by approximately 125 patients in Cohort A, for a total of approximately 715 patients (Phase 1 N≈110; Phase 2 N≈605). |
| 03 August 2016 | Discontinuation of the rociletinib clinical development program prompted the introduction of a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that would no longer be analyzed or required for regulatory purposes, while maintaining an appropriate level of safety monitoring. A detailed description of the study design and Schedule of Assessments is provided in the Protocol Amendment 8. Through Protocol Amendment 7, response was determined by both investigator assessment (primary endpoint) and IRR (secondary endpoint). Starting in Amendment 8 (Extension Phase), tumor scans were only interpreted locally by the investigator for final tumor response evaluation. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 12 May 2016 | Enrollment to the trial ended due to a corporate decision to suspend the development of rociletinib. Patients who were in screening as of 05 May 2016 could enroll on or before 12 May 2016 if they met eligibility requirements.<br><br>As of that date, a total of 612 patients had enrolled in Study CO-1686-008, with 50 active patients; 42 sites had screened at least 1 patient, and 29 of these sites had enrolled at least 1 patient. As of 27 August 2018, there were no patients remaining on study. The last patient on study (Patient 526609) had her last study visit on 16 August 2018 and died on 27 August 2018. Her last dose of rociletinib was on 26 August 2018. All 49 sites were closed, and the database lock was completed on 13 December 2018. | - |

Notes:

## Limitations and caveats

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

| |
|---|
| The following endpoints are not reported since they were not analyzed due to early study termination: ORR, DOR, PFS as determined by independent radiology review. |

Notes: