



Clinical trial results:

A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study of ARQ 197 Plus Erlotinib Versus Placebo Plus Erlotinib in Previously Treated Subjects with Locally Advanced or Metastatic, Non-Squamous, Non-Small-Cell Lung Cancer (NSCLC)

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2010-022365-10 |
| Trial protocol | HU CZ DE ES IT SE GB DK AT BE |
| Global end of trial date | 06 October 2016 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 20 March 2018 |
| First version publication date | 20 March 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | ARQ197-A-U302 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01244191 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Daiichi Sankyo, Inc. |
| Sponsor organisation address | 211 Mt. Airy Road, Basking Ridge, United States, 07920 |
| Public contact | Clinical Trial Information, Daiichi Sankyo Development Limited, +44 1753482800, info@dsd-eu.com |
| Scientific contact | Clinical Trial Information, Daiichi Sankyo Development Limited, +44 1753482800, info@dsd-eu.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 | 30 November 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 October 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate overall survival (OS) in the intent-to-treat (ITT) subject population defined by this protocol.

Protection of trial subjects:

This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s). Dose delays and/or reductions were permitted.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 11 January 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 4 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 67 |
| Country: Number of subjects enrolled | United States: 229 |
| Country: Number of subjects enrolled | Chile: 17 |
| Country: Number of subjects enrolled | Argentina: 14 |
| Country: Number of subjects enrolled | Australia: 17 |
| Country: Number of subjects enrolled | Brazil: 45 |
| Country: Number of subjects enrolled | Canada: 39 |
| Country: Number of subjects enrolled | Mexico: 10 |
| Country: Number of subjects enrolled | Peru: 11 |
| Country: Number of subjects enrolled | Poland: 78 |
| Country: Number of subjects enrolled | Romania: 13 |
| Country: Number of subjects enrolled | Spain: 79 |
| Country: Number of subjects enrolled | Netherlands: 12 |
| Country: Number of subjects enrolled | Sweden: 2 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Austria: 1 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Czech Republic: 8 |
| Country: Number of subjects enrolled | Denmark: 14 |
| Country: Number of subjects enrolled | France: 101 |
| Country: Number of subjects enrolled | Germany: 93 |
| Country: Number of subjects enrolled | Hungary: 31 |
| Country: Number of subjects enrolled | Italy: 152 |
| Worldwide total number of subjects | 1048 |
| EEA total number of subjects | 599 |

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) | 646 |
| From 65 to 84 years | 399 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Between Jan 2011 and July 2012, of the 1624 patients screened, 1048 were randomized to treatment and formed the Intent-to-treat (ITT) Population.

Results of the interim analysis met the protocol-defined stopping criteria.

Protocol amendment 4 allowed only the EGFR mutant subgroup to continue (indicated here as Period 2).

Pre-assignment

Screening details:

A total of 1624 subjects were screened for this study in 23 countries.

Period 1

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

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Erlotinib plus tivantinib |

Arm description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg).

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

Dosage and administration details:

Single tablet once daily at least 1 hour before or at least 2 hours after food.

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

Dosage and administration details:

Three 120 mg tablets twice daily with meals, for a total daily dose of 720 mg.

| | |
|------------------|------------------------|
| Arm title | Erlotinib plus placebo |
|------------------|------------------------|

Arm description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals.

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

Dosage and administration details:

Single tablet once daily at least 1 hour before or at least 2 hours after food.

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

Dosage and administration details:

Three tablets twice daily with meals.

| Number of subjects in period 1 | Erlotinib plus tivantinib | Erlotinib plus placebo |
|--|------------------------------|---------------------------|
| Started | 526 | 522 |
| Treated - safety analysis set | 520 | 517 |
| Completed | 46 | 24 |
| Not completed | 480 | 498 |
| Consent withdrawn by subject | 31 | 23 |
| Missing or study terminated by sponsor | 12 | 8 |
| Adverse event, non-fatal | 65 | 48 |
| Death | 22 | 29 |
| Clinical disease progression | 54 | 36 |
| Progressive disease | 295 | 350 |
| Lost to follow-up | - | 2 |
| Protocol deviation | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Erlotinib plus tivantinib |
|-----------------------|---------------------------|

Reporting group description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg).

| | |
|-----------------------|------------------------|
| Reporting group title | Erlotinib plus placebo |
|-----------------------|------------------------|

Reporting group description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals.

| Reporting group values | Erlotinib plus tivantinib | Erlotinib plus placebo | Total |
|------------------------|---------------------------|------------------------|-------|
| Number of subjects | 526 | 522 | 1048 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 320 | 326 | 646 |
| From 65-84 years | 204 | 195 | 399 |
| 85 years and over | 2 | 1 | 3 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 61.2 | 61.1 | |
| standard deviation | ± 10.10 | ± 9.84 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 216 | 213 | 429 |
| Male | 310 | 309 | 619 |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | Erlotinib plus tivantinib |
| Reporting group description: Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg). | |
| Reporting group title | Erlotinib plus placebo |
| Reporting group description: Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals. | |

Primary: Overall survival (OS) in Original Intent-to-treat (ITT) Population

| | |
|---|--|
| End point title | Overall survival (OS) in Original Intent-to-treat (ITT) Population |
| End point description: Median length of time patients survived | |
| End point type | Primary |
| End point timeframe: by study completion, within 5 years, 9 months | |

| End point values | Erlotinib plus tivantinib | Erlotinib plus placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 526 | 522 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.5 (7.1 to 9.3) | 7.8 (7.0 to 9.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Original ITT - OS Analysis |
| Comparison groups | Erlotinib plus tivantinib v Erlotinib plus placebo |
| Number of subjects included in analysis | 1048 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.8086 ^[1] |
| Method | Logrank |

Notes:

[1] - p-value from the stratified log-rank test [adjusting for number of prior therapies, gender, and smoking history using the IXRS (Randomization) data set] provides an overall comparison of the OS survival curves.

Secondary: Progression-Free Survival (PFS) in the Original ITT Population

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) in the Original ITT Population |
|-----------------|--|

| | |
|---|-----------|
| End point description: | |
| Kaplan-Meier estimates of the median PFS times for each treatment group | |
| End point type | Secondary |
| End point timeframe: | |
| by study completion, within 5 years, 9 months | |

| End point values | Erlotinib plus tivantinib | Erlotinib plus placebo | | |
|----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 526 | 522 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.6 (2.8 to 3.7) | 1.9 (1.9 to 2.0) | | |

Statistical analyses

| Statistical analysis title | Period 1 Original ITT |
|---|--|
| Comparison groups | Erlotinib plus tivantinib v Erlotinib plus placebo |
| Number of subjects included in analysis | 1048 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 ^[2] |
| Method | Logrank |

Notes:

[2] - p-value from the stratified log-rank test (adjusting for number of prior therapies, gender, and smoking history using the IXRS data set) provides an overall comparison of the PFS survival curves

Other pre-specified: Overall Survival in the EGFR Mutant Subpopulation (ITT)

| | |
|---|---|
| End point title | Overall Survival in the EGFR Mutant Subpopulation (ITT) |
| End point description: | |
| Median length of time patients survived who were in the EGFR-mutant sub-population that continued until November 2014 | |
| End point type | Other pre-specified |
| End point timeframe: | |
| by study completion, within 5 years, 9 months | |

| End point values | Erlotinib plus tivantinib | Erlotinib plus placebo | | |
|----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 53 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 25.5 (15.6 to 38.9) | 20.3 (16.6 to 24.3) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EGFR-Mutant Analysis |
| Statistical analysis description: Analysis of EGFR-mutant patients who continued during Amended Protocol 4 | |
| Comparison groups | Erlotinib plus tivantinib v Erlotinib plus placebo |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.1013 ^[3] |
| Method | Logrank |

Notes:

[3] - p-value from the stratified log-rank test (adjusting for number of prior therapies, gender, and smoking history) provides an overall comparison of the PFS survival curves

Other pre-specified: Progression-Free Survival in the EGFR Mutant Subpopulation (ITT)

| | |
|---|--|
| End point title | Progression-Free Survival in the EGFR Mutant Subpopulation (ITT) |
| End point description: Kaplan-Meier estimates of the median PFS times for each treatment group | |
| End point type | Other pre-specified |
| End point timeframe: by study completion, within 5 years, 9 months | |

| End point values | Erlotinib plus tivantinib | Erlotinib plus placebo | | |
|----------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 56 | 53 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 13.0 (7.3 to 17.7) | 7.5 (5.6 to 11.9) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were collected until 30 days after completing treatment, within 5 years, 9 months.

TEAEs that occurred more than 30 days after the last dose of study medication are not included unless related to treatment.

Adverse event reporting additional description:

At each level of summarizing TEAEs, a patient was counted only once if he/she reported one or more adverse events in this older trial. Therefore, the number of events mirrors the number of patients. Relatedness is based on the experimental products placebo and tivantinib only.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 13.1 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Erlotinib plus placebo |
|-----------------------|------------------------|

Reporting group description: -

| | |
|-----------------------|---------------------------|
| Reporting group title | Erlotinib plus tivantinib |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events | Erlotinib plus placebo | Erlotinib plus tivantinib | |
|---|------------------------|---------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 198 / 517 (38.30%) | 228 / 520 (43.85%) | |
| number of deaths (all causes) | 300 | 314 | |
| number of deaths resulting from adverse events | 67 | 82 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 4 / 517 (0.77%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant ascites | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Metastases to central nervous system | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lymph nodes | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to spleen | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic pain | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Paraneoplastic syndrome | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour compression | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism arterial | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Superior vena caval occlusion | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous insufficiency | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 517 (0.97%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 13 / 517 (2.51%) | 16 / 520 (3.08%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 7 | 0 / 10 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ disorder | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Performance status decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 517 (0.58%) | 5 / 520 (0.96%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 517 (0.97%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute lung injury | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 4 / 517 (0.77%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse alveolar damage | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 24 / 517 (4.64%) | 28 / 520 (5.38%) | |
| occurrences causally related to treatment / all | 2 / 24 | 0 / 28 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 11 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 4 / 517 (0.77%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinal disorder | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthopnoea | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 9 / 517 (1.74%) | 13 / 520 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleurisy | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumomediastinum | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 5 / 520 (0.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 20 / 517 (3.87%) | 17 / 520 (3.27%) | |
| occurrences causally related to treatment / all | 4 / 20 | 2 / 17 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory arrest | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 9 / 517 (1.74%) | 12 / 520 (2.31%) | |
| occurrences causally related to treatment / all | 1 / 9 | 1 / 12 | |
| deaths causally related to treatment / all | 0 / 8 | 1 / 8 | |
| Tracheal stenosis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coagulation test abnormal | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Collapse of lung | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug toxicity | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 517 (0.58%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pericardial haemorrhage | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis constrictive | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain compression | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 4 / 517 (0.77%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Coma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Convulsion | | | |
| subjects affected / exposed | 5 / 517 (0.97%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Demyelination | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epiduritis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Headache | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological decompensation | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 517 (1.35%) | 16 / 520 (3.08%) | |
| occurrences causally related to treatment / all | 2 / 7 | 11 / 16 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 15 / 520 (2.88%) | |
| occurrences causally related to treatment / all | 0 / 2 | 11 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 12 / 520 (2.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 12 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic obstruction | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 517 (1.35%) | 4 / 520 (0.77%) | |
| occurrences causally related to treatment / all | 2 / 7 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal perforation | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 517 (0.39%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal infarction | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 6 / 517 (1.16%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal disorder | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 517 (0.97%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Nail toxicity | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous nodule | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 5 / 520 (0.96%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 5 / 517 (0.97%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 3 / 520 (0.58%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Cystitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 4 / 517 (0.77%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 13 / 517 (2.51%) | 22 / 520 (4.23%) | |
| occurrences causally related to treatment / all | 1 / 13 | 2 / 22 | |
| deaths causally related to treatment / all | 1 / 3 | 1 / 3 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyothorax | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 517 (0.39%) | 6 / 520 (1.15%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 4 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Skin infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 517 (0.58%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 517 (0.19%) | 0 / 520 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 7 / 517 (1.35%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 2 / 7 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 517 (0.77%) | 5 / 520 (0.96%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 517 (0.00%) | 1 / 520 (0.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 517 (0.00%) | 2 / 520 (0.38%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Erlotinib plus placebo | Erlotinib plus tivantinib | |
|---|------------------------|---------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 496 / 517 (95.94%) | 505 / 520 (97.12%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 59 / 517 (11.41%) | 59 / 520 (11.35%) | |
| occurrences (all) | 59 | 59 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 29 / 517 (5.61%) | 43 / 520 (8.27%) | |
| occurrences (all) | 29 | 43 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 113 / 517 (21.86%) | 139 / 520 (26.73%) | |
| occurrences (all) | 113 | 139 | |
| Asthenia | | | |
| subjects affected / exposed | 91 / 517 (17.60%) | 101 / 520 (19.42%) | |
| occurrences (all) | 91 | 101 | |
| Pyrexia | | | |
| subjects affected / exposed | 41 / 517 (7.93%) | 62 / 520 (11.92%) | |
| occurrences (all) | 41 | 62 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 30 / 517 (5.80%) | 40 / 520 (7.69%) | |
| occurrences (all) | 30 | 40 | |
| Non-cardiac chest pain | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 23 / 517 (4.45%) 23 | 35 / 520 (6.73%) 35 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 24 / 517 (4.64%) 24 | 29 / 520 (5.58%) 29 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 48 / 517 (9.28%) 48 | 78 / 520 (15.00%) 78 | |
| Neutropenia subjects affected / exposed occurrences (all) | 11 / 517 (2.13%) 11 | 57 / 520 (10.96%) 57 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 215 / 517 (41.59%) 215 | 181 / 520 (34.81%) 181 | |
| Nausea subjects affected / exposed occurrences (all) | 123 / 517 (23.79%) 123 | 123 / 520 (23.65%) 123 | |
| Vomiting subjects affected / exposed occurrences (all) | 81 / 517 (15.67%) 81 | 77 / 520 (14.81%) 77 | |
| Constipation subjects affected / exposed occurrences (all) | 54 / 517 (10.44%) 54 | 58 / 520 (11.15%) 58 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 26 / 517 (5.03%) 26 | 35 / 520 (6.73%) 35 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 24 / 517 (4.64%) 24 | 31 / 520 (5.96%) 31 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 19 / 517 (3.68%) 19 | 33 / 520 (6.35%) 33 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--------------------|--------------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 102 / 517 (19.73%) | 128 / 520 (24.62%) | |
| occurrences (all) | 102 | 128 | |
| Cough | | | |
| subjects affected / exposed | 95 / 517 (18.38%) | 115 / 520 (22.12%) | |
| occurrences (all) | 95 | 115 | |
| Haemoptysis | | | |
| subjects affected / exposed | 15 / 517 (2.90%) | 30 / 520 (5.77%) | |
| occurrences (all) | 15 | 30 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 193 / 517 (37.33%) | 173 / 520 (33.27%) | |
| occurrences (all) | 193 | 173 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 98 / 517 (18.96%) | 91 / 520 (17.50%) | |
| occurrences (all) | 98 | 91 | |
| Dry skin | | | |
| subjects affected / exposed | 57 / 517 (11.03%) | 42 / 520 (8.08%) | |
| occurrences (all) | 57 | 42 | |
| Pruritus | | | |
| subjects affected / exposed | 45 / 517 (8.70%) | 32 / 520 (6.15%) | |
| occurrences (all) | 45 | 32 | |
| Alopecia | | | |
| subjects affected / exposed | 14 / 517 (2.71%) | 27 / 520 (5.19%) | |
| occurrences (all) | 14 | 27 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 29 / 517 (5.61%) | 34 / 520 (6.54%) | |
| occurrences (all) | 29 | 34 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 47 / 517 (9.09%) | 55 / 520 (10.58%) | |
| occurrences (all) | 47 | 55 | |
| Pain in extremity | | | |
| subjects affected / exposed | 19 / 517 (3.68%) | 31 / 520 (5.96%) | |
| occurrences (all) | 19 | 31 | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 149 / 517 (28.82%) | 152 / 520 (29.23%) | |
| occurrences (all) | 149 | 152 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 20 October 2010 | <ul style="list-style-type: none">- Revised to require prior platinum-doublet therapy, and clarify eligibility requirements for subjects with prior adjuvant or maintenance therapy- Specified that subjects who experienced \geq Grade 3 neutropenia were to be monitored closely throughout study and offered hematopoietic growth factor therapy as per ASCO guidelines. Also, increased frequency of ANC monitoring for Cycles 3+ from every 4 weeks to every 2 weeks for all subjects, not only those receiving CYP 2C19 or CYP 3A4 inhibitors.- Added precaution for potential of concomitant medications altering gastric pH to affect erlotinib absorption- Added fluconazole, ticlopidine, rabeprazole, and fluoxetine to list of example CYP 2C19 inhibitors to be used with caution concomitantly- Clarified that AEs recorded at Screening visit were to include only those AEs occurring after consent was signed- Removed qualification "if not restricted by local regulation" to require collection of pharmacogenomic data at all sites- Modified language to specify that hematology testing would be performed for all subjects every 2 weeks rather than every 4 weeks in Cycle 3 and beyond- Removed limit of precaution to only "strong" CYP 2C19 inhibitors, but clarified limit to precaution for only strong inhibitors of CYP 3A4- Specified requirement for biomarker testing for tumor MET, EGFR, and KRAS for all subjects, as well as testing for pre- and posttreatment circulating HGF- Added language specifying data sets and analyses for pharmacogenomic data and PK-pharmacodynamic analyses |
| 01 June 2011 | <ul style="list-style-type: none">- Added exception for enrollment of subjects with \leq Grade 2 neuropathy- Reduced window for prior surgical procedure, prior systemic anti-tumor therapy, and prior radiotherapy from 4 weeks to 3 weeks- Clarified description of exploratory objectives, endpoints, and analyses with regard to MET status as determined by IHC and FISH. Specifically, the exploratory analysis for evaluating OS and PFS by MET/MET was to be performed using both IHC and FISH analytical methods instead of FISH method only.- Clarified that either archival or fresh tissue biopsy samples would qualify for study eligibility; documented EGFR and KRAS status must have been from an accredited lab; specified that tissue must be provided to central laboratories for MET analysis even if EGFR, KRAS results were obtained locally- Noted that EGFR status was required for study eligibility; in the absence of confirmation of a subject's KRAS status, the subject was to be categorized as "indeterminate" for KRAS- Added exception to the prohibition of highdose corticosteroids for short-term treatment of COPD or other inflammation exacerbation |

| | |
|------------------|---|
| 28 November 2012 | <ul style="list-style-type: none"> - Revised text to indicate that only subjects with EGFR-mutant disease would be included in survival followup evaluations - Revised text to indicate that study closure was to be defined as the final subject visit/contact rather than when the pre-specified 735 deaths have occurred <p>The interim results for this study met the protocol-defined stopping boundary for futility based on overall survival (OS). After reviewing the interim analysis, the data management committee (DMC) concluded that the study would not meet its primary endpoint of improved OS in the intent to treat (ITT) population, and therefore recommended that the study be stopped early. However, the DMC noted that there was no unexpected safety concern requiring immediate treatment discontinuation, and there was a trend toward improvement in progression free survival (PFS) in the ITT population at the interim analysis. Based upon this result, the data were cut on 15 Dec 2012 for the main study analyses included in the original CSR. Patients receiving clinical benefit were allowed to continue. At the time of the data-cut for the main study analyses, the results for EGFR mutant subgroup, which responds well to erlotinib therapy, were not mature. The clinical trial protocol was amended to allow these subjects to continue with follow-up assessments in order to provide mature results for this subgroup.</p> <p>The results posted herein incorporate the tables, figures, and listings for the pre-specified data-cut (Nov 2014) for the EGFR mutant subgroup. This clinical study has now been completed and the full database is locked. This record also includes the isolated EGFR mutant data that were collected during the study.</p> |
|------------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported