# Clinical trial results:
# Study VEG108844, A study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma

## Summary

| | |
|---|---|
| EudraCT number | 2008-002102-19 |
| Trial protocol | IE GB ES SE NL IT DE |
| Global end of trial date | 24 March 2021 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 16 April 2025 |
| First version publication date | 06 April 2022 |
| Version creation reason | |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 108844 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00720941 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Novartis: CPZP034A2301, GlaxoSmithKline: VEG108844 |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 24 March 2021 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 March 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival of subjects treated with pazopanib to those treated with sunitinib.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 August 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 51 |
| Country: Number of subjects enrolled | Canada: 46 |
| Country: Number of subjects enrolled | China: 209 |
| Country: Number of subjects enrolled | Germany: 55 |
| Country: Number of subjects enrolled | Ireland: 17 |
| Country: Number of subjects enrolled | Italy: 36 |
| Country: Number of subjects enrolled | Japan: 61 |
| Country: Number of subjects enrolled | Korea, Republic of: 68 |
| Country: Number of subjects enrolled | Netherlands: 19 |
| Country: Number of subjects enrolled | Spain: 41 |
| Country: Number of subjects enrolled | Sweden: 16 |
| Country: Number of subjects enrolled | Taiwan: 29 |
| Country: Number of subjects enrolled | United Kingdom: 126 |
| Country: Number of subjects enrolled | United States: 336 |
| Worldwide total number of subjects | 1110 |
| EEA total number of subjects | 184 |

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) | 676 |
| From 65 to 84 years | 428 |
| 85 years and over | 6 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants were stratified based on Karnofsky Performance Scale scores (70 or 80; 90 or 100), Baseline levels of lactate dehydrogenase (>1.5 versus <=1.5 times the upper limit of normal [ULN]), and previous nephrectomy (yes versus no) and were randomized in a 1:1 ratio to receive either pazopanib or sunitinib.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Pazopanib 800 mg |

Arm description:

Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pazopanib |
| Investigational medicinal product code | |
| Other name | GW786034 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

800 mg (2 x 400 mg tablets or 4 x 200 mg tablets) administered orally once daily (continuously) at least 1 hour before or at least 2 hours after a meal.

| | |
|---|---|
| **Arm title** | Sunitinib 50 mg |

Arm description:

Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Sunitinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

50 mg administered in 6-week cycles orally once daily with or without food, for 4 weeks of treatment followed by 2 weeks without treatment.

| **Number of subjects in period 1** | Pazopanib 800 mg | Sunitinib 50 mg |
|---|---|---|
| Started | 557 | 553 |
| Safety Population | 554 | 548 |
| Completed | 485 | 481 |
| Not completed | 72 | 72 |
| Physician decision | 14 | 12 |
| Consent withdrawn by subject | 29 | 36 |
| Lost to follow-up | 20 | 15 |
| Protocol deviation | 1 | 2 |
| Transitioned to another mechanism of cont. therapy | 8 | 7 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pazopanib 800 mg |
| Reporting group description: | |
| Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons. | |
| Reporting group title | Sunitinib 50 mg |
| Reporting group description: | |
| Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons. | |

| Reporting group values | Pazopanib 800 mg | Sunitinib 50 mg | Total |
|---|---|---|---|
| Number of subjects | 557 | 553 | 1110 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 344 | 332 | 676 |
| From 65-84 years | 208 | 220 | 428 |
| 85 years and over | 5 | 1 | 6 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 159 | 138 | 297 |
| Male | 398 | 415 | 813 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 349 | 358 | 707 |
| Asian | 194 | 188 | 382 |
| African American/African Heritage | 10 | 5 | 15 |
| American Indian or Alaska Native | 3 | 0 | 3 |
| American Indian or Alaska Native & White | 0 | 1 | 1 |
| Unknown | 1 | 1 | 2 |
| GenderNIH<br>Units: Subjects | | | |
| Female | 159 | 138 | 297 |
| Male | 398 | 415 | 813 |
| AgeContinuous<br>Units: Years | | | |
| arithmetic mean | 60.9 | 61.2 | |
| standard deviation | ± 10.89 | ± 10.98 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Pazopanib 800 mg |

Reporting group description:

Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

| | |
|---|---|
| Reporting group title | Sunitinib 50 mg |

Reporting group description:

Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

### Primary: Progression-free Survival (PFS)

| | |
|---|---|
| End point title | Progression-free Survival (PFS) |

End point description:

PFS was defined as the interval between the date of randomization and the earliest date of progressive disease (PD), as defined by the Independent Review Committee (IRC), or death due to any cause. The IRC defined PD per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1. Per RECIST, PD is defined as a >=20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of >=1 new lesion.

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

End point timeframe:

From randomization until the earliest date of disease progression or date of death from any cause, assessed up to approximately 39 months

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 557 | 553 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 8.4 (8.3 to 10.9) | 9.5 (8.3 to 11.1) | | |

### Statistical analyses

| Statistical analysis title | Progression-free Survival (PFS) |
|---|---|
| Comparison groups | Pazopanib 800 mg v Sunitinib 50 mg |

| | |
|---|---|
| Number of subjects included in analysis | 1110 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.0466 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8982 |
| upper limit | 1.2195 |

## Secondary: Overall Survival

| | |
|---|---|
| End point title | Overall Survival |

End point description:

Overall survival was defined as the time from randomization until death due to any cause.

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

End point timeframe:

From randomization until date of death from any cause, assessed up to approximately 62 months

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 557 | 553 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 28.3 (26.0 to 35.5) | 29.1 (25.4 to 33.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (ORR) as assessed by independent review

| | |
|---|---|
| End point title | Overall Response Rate (ORR) as assessed by independent review |

End point description:

The number of participants with evidence of Complete Response (CR) (the disappearance of all target and non-target lesions), Partial Response (PR) (at least a 30% decrease in the sum of the longest diameters [LD] of target lesions, taking as a reference the Baseline sum LD), Stable Disease (small changes that do not meet previously given criteria, taking as reference the smallest sum LD since the treatment started), or Progressive Disease (a >=20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started) was evaluated by an independent review per RECIST, Version 1.

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

End point timeframe:

From randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 39 months

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 557 | 553 | | |
| Units: Participants | | | | |
| Complete Response | 1 | 3 | | |
| Partial Response | 170 | 134 | | |
| Stable Disease | 216 | 242 | | |
| Progressive Disease | 97 | 105 | | |
| Unknown | 73 | 69 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response

| End point title | Time to Response |
|---|---|

End point description:

Time to response was defined as the time from the start of treatment until the first documented evidence of CR (the disappearance of all target and non-target lesions) or PR (at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the Baseline sum LD), whichever comes first. CR and PR were evaluated by an independent review per RECIST, Version 1.

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

End point timeframe:

From randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 39 months

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 137 | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 11.9 (11.3 to 12.1) | 17.4 (12.7 to 18.0) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR)

| End point title | Duration of Response (DOR) |
|---|---|

End point description:

DOR was defined as the time from the first documented evidence of response (CR or PR) until the first documented sign of disease progression (a >=20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of >=1 new lesion) or death, if sooner. CR=the disappearance of all target and non-target lesions. PR=at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the Baseline sum LD.

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

End point timeframe:

From the date of the first documented response (CR or PR) to the date of first documented progression or death due to any cause, assessed up to approximately 39 months

| **End point values** | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 137 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 13.8 (12.2 to 16.4) | 18.0 (14.3 to 22.1) | | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale scores at Day 28 of Cycles 1-4

| End point title | Change from Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale scores at Day 28 of Cycles 1-4 |
|---|---|

End point description:

FACIT Fatigue Subscale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued). The total score range is from 0-52. The higher the score, the lower the fatigue level.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| **End point values** | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 353 | 375 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=353,375) | -5.3 (± 11.00) | -6.7 (± 10.93) | | |
| Week 10 (n=293,330) | -4.0 (± 10.28) | -6.3 (± 10.65) | | |
| Week 16 (n=273,280) | -3.8 (± 10.13) | -6.9 (± 11.16) | | |
| Week 22 (n=227,240) | -2.9 (± 9.77) | -6.5 (± 10.51) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with Adverse Events

| End point title | Number of participants with Adverse Events |
|---|---|

End point description:

The distribution of adverse events was done via the analysis of frequencies for Adverse Event (AEs) and Serious Adverse Event (SAEs), through the monitoring of relevant clinical and laboratory safety parameters.

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

End point timeframe:

From study treatment start date till 28 days safety follow-up, assessed up to approximately 152 months

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: Participants | | | | |
| Adverse Events (AEs) | 551 | 535 | | |
| Serious Adverse Events (SAEs) | 242 | 227 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease-related symptoms-physical (DRS-P) domain score at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease-related symptoms-physical (DRS-P) domain score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total score of 0 to 76). A negative mean indicates a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 358 | 378 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=358,378) | -2.9 (± 6.39) | -3.9 (± 6.87) | | |
| Week 10 (n=296,336) | -2.3 (± 6.69) | -3.2 (± 6.76) | | |
| Week 16 (n=269,283) | -2.6 (± 6.70) | -3.2 (± 6.61) | | |
| Week 22 (n=224,238) | -1.3 (± 6.29) | -2.7 (± 6.42) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease related symptoms-emotional (DRS-E) domain score at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease related symptoms-emotional (DRS-E) domain score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total score of 0 to 76). A negative mean indicates a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 344 | 367 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=344,367) | 0.3 (± 1.31) | 0.4 (± 1.22) | | |
| Week 10 (n=287,329) | 0.4 (± 1.33) | 0.5 (± 1.32) | | |
| Week 16 (n=260,277) | 0.5 (± 1.39) | 0.6 (± 1.30) | | |
| Week 22 (n=220,233) | 0.6 (± 1.27) | 0.6 (± 1.20) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale treatment side effects (TSE) domain score at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale treatment side effects (TSE) domain score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total score of 0 to 76). A negative mean indicates a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 350 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=326,350) | -1.5 (± 2.45) | -2.0 (± 2.35) | | |
| Week 10 (n=267,305) | -1.9 (± 2.66) | -2.4 (± 2.62) | | |
| Week 16 (n=244,254) | -2.1 (± 2.79) | -2.8 (± 2.46) | | |
| Week 22 (n=201,218) | -2.4 (± 2.75) | -2.4 (± 2.33) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale functional well being (FWB) domain score at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale functional well being (FWB) domain score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total score of 0 to 76). A negative mean indicates a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| **End point values** | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 357 | 378 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=357,378) | -1.0 (± 4.01) | -1.3 (± 3.63) | | |
| Week 10 (n=298,331) | -0.6 (± 4.00) | -1.1 (± 3.94) | | |
| Week 16 (n=267,278) | -0.8 (± 4.08) | -1.0 (± 3.96) | | |
| Week 22 (n=228,234) | -0.7 (± 3.93) | -1.0 (± 3.82) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale total score at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale total score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total score of 0 to 76). A negative mean indicates a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 358 | 379 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=358,379) | -5.0 (± 10.82) | -6.6 (± 10.55) | | |
| Week 10 (n=296,337) | -4.2 (± 10.95) | -6.3 (± 11.21) | | |
| Week 16 (n=267,284) | -4.8 (± 11.13) | -6.3 (± 10.67) | | |
| Week 22 (n=225,238) | -3.7 (± 10.49) | -5.5 (± 10.13) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) scale worst soreness scores at Day 28 of Cycles 1-4

| End point title | Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) scale worst soreness scores at Day 28 of Cycles 1-4 |
|---|---|

End point description:

The SQLQ scale consists of 5 items that assess the worst mouth and throat, hand, and foot soreness, as well as limitations due to mouth/throat and foot soreness. Participants were asked to assess their worst mouth/throat, hand, and foot soreness by answering the question of " In the past 4 weeks, what was your worst mouth/throat, hand, and foot soreness?" by using the following 4-point scale: 0, I never had any soreness; 1, I had a little bit of soreness; 2, I had quite a lot of soreness; 3, I had severe soreness. A positive mean change from Baseline represents a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 202 | 184 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mouth and Throat Soreness, Week 4 (n=202,180) | 0.4 (± 0.87) | 1.0 (± 0.99) | | |
| Mouth and Throat Soreness, Week 10 (n=164,155) | 0.4 (± 0.88) | 0.9 (± 0.99) | | |
| Mouth and Throat Soreness, Week 16 (n=137,138) | 0.3 (± 0.73) | 0.8 (± 0.89) | | |
| Mouth and Throat Soreness, Week 22 (n=120,117) | 0.2 (± 0.75) | 0.8 (± 0.81) | | |
| Hand Soreness, Week 4 (n=200,184) | 0.2 (± 0.71) | 0.3 (± 0.72) | | |
| Hand Soreness, Week 10 (n=164,153) | 0.3 (± 0.84) | 0.7 (± 0.85) | | |
| Hand Soreness, Week 16 (n=139,136) | 0.4 (± 0.76) | 0.6 (± 0.80) | | |
| Hand Soreness, Week 22 (n=123,115) | 0.3 (± 0.69) | 0.6 (± 0.82) | | |
| Foot Soreness, Week 4 (n=199,182) | 0.2 (± 0.86) | 0.4 (± 0.80) | | |

| | | | | |
|---|---|---|---|---|
| Foot Soreness, Week 10 (n=163,153) | 0.3 (± 1.00) | 0.6 (± 0.99) | | |
| Foot Soreness, Week 16 (n=140,136) | 0.3 (± 1.07) | 0.8 (± 0.99) | | |
| Foot Soreness, Week 22 (n=123,116) | 0.3 (± 1.04) | 0.9 (± 0.96) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) limitations due to mouth and throat soreness score at Day 28 of Cycles 1-4

| | |
|---|---|
| End point title | Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) limitations due to mouth and throat soreness score at Day 28 of Cycles 1-4 |

End point description:

The SQLQ consists of 5 items assessing the worst mouth/throat, hand, and foot soreness, and limitations due to mouth/throat and foot soreness. Participants assessed the limitations caused by their mouth/throat soreness by answering the question of "In the past 4 weeks, how much did your worst mouth/throat soreness limit you in the following activities: swallowing/eating/drinking/talking/sleeping" by using the following 4-point scale: 0, not limited; 1, limited a little; 2, limited a lot; 3, unable to do. The overall limitation score (15=best; 0=worst), based on the individual scores for the 5 activities, is derived as follows: the actual scores were rescored by subtracting the actual score from "3" for each of the 5 categories. A high score indicates less limitation. Change from Baseline was calculated as the assessment week value minus the Baseline value. A negative mean change from Baseline represents a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 177 | 170 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=177,170) | -0.9 (± 2.09) | -1.8 (± 2.91) | | |
| Week 10 (n=144,137) | -0.9 (± 1.91) | -1.8 (± 3.06) | | |
| Week 16 (n=125,122) | -0.6 (± 1.56) | -1.3 (± 2.30) | | |
| Week 22 (n=111,107) | -0.4 (± 1.67) | -1.4 (± 1.85) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the Supplementary Quality of Life Questions (SQLQ) Limitations Due to Foot Soreness Scores at Day 28 of Cycles 1-4

| | |
|---|---|
| End point title | Change From Baseline in the Supplementary Quality of Life Questions (SQLQ) Limitations Due to Foot Soreness Scores at Day 28 of Cycles 1-4 |

End point description:

The SQLQ consists of 5 items assessing the worst mouth/throat, hand, and foot soreness, and limitations due to mouth/throat and foot soreness. Participants assessed the limitations caused by their foot soreness by answering the question of "In the past 4 weeks, how much did your worst foot soreness limit you in each of the following activities: standing/walking/climbing stairs/sleeping/ability to do usual activities" by using the following 4-point scale: 0, not limited; 1, limited a little; 2, limited a lot; 3, unable to do. The overall limitation score (15=best; 0=worst), based on the individual scores for the 5 activities, is derived as follows: the actual scores were rescored by subtracting the actual score from "3" for each of the 5 categories. A high score indicates less limitation. Change from Baseline was calculated as the assessment week value minus the Baseline value. A negative mean change from Baseline represents a worsening of condition.

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

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| **End point values** | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 170 | 163 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=170,163) | -0.6 (± 2.94) | -1.0 (± 2.94) | | |
| Week 10 (n=133,136) | -1.1 (± 3.02) | -1.5 (± 3.76) | | |
| Week 16 (n=114,126) | -1.2 (± 3.42) | -2.2 (± 3.50) | | |
| Week 22 (n=105,108) | -1.3 (± 3.25) | -2.1 (± 3.52) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Analysis for the Cancer Treatment Satisfaction Questionnaire (CTSQ) Score at Day 28 of Cycles 1-4

| End point title | Summary of Analysis for the Cancer Treatment Satisfaction Questionnaire (CTSQ) Score at Day 28 of Cycles 1-4 |
|---|---|

End point description:

The CTSQ assesses 3 domains related to the participant’s satisfaction with cancer therapy: Expectations of Therapy (ET), Feelings about Side Effects (FSE), and Satisfaction with Therapy (SWT). Participants shared their thoughts on their cancer therapy (9 questions), their satisfaction with their most recently administered cancer therapy (6 questions), and if they would take the same cancer therapy if given the choice to do so again. All questions were assessed on a 5-point scale; 1, never; 5, always. Scores were averaged and transformed to a 0-100 scale; higher scores represent better treatment satisfaction.

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

End point timeframe:

Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 383 | 386 | | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| ET, Week 4 (n=383,386) | 71.7 (± 22.13) | 71.3 (± 22.38) | | |
| ET, Week 10 (n=321,346) | 73.4 (± 21.62) | 73.4 (± 19.37) | | |
| ET, Week 16 (n=296,293) | 73.9 (± 21.56) | 72.9 (± 21.43) | | |
| ET, Week 22 (n=250,250) | 73.0 (± 21.40) | 73.4 (± 20.43) | | |
| FSE, Week 4 (n=340,360) | 66.3 (± 24.00) | 58.5 (± 23.59) | | |
| FSE, Week 10 (n=298,323) | 66.0 (± 23.09) | 56.0 (± 22.23) | | |
| FSE, Week 16 (n=274,277) | 65.0 (± 23.01) | 56.6 (± 22.02) | | |
| FSE, Week 22 (n=235, 232) | 67.1 (± 22.62) | 57.8 (± 21.28) | | |
| SWT, Week 4 (n=355,374) | 80.9 (± 15.49) | 79.0 (± 15.23) | | |
| SWT, Week 10 (n=309,336) | 84.5 (± 13.74) | 80.4 (± 15.15) | | |
| SWT, Week 16 (n=287,284) | 85.3 (± 14.77) | 80.5 (± 15.08) | | |
| SWT, Week 22 (n=241,240) | 85.4 (± 13.48) | 81.4 (± 15.04) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Number of Non-study Medical Visits, Telephone Consultations, Hospital Days, and Emergency Room (ER) Visits Per 30 Days Through Week 24

| End point title | Mean Number of Non-study Medical Visits, Telephone Consultations, Hospital Days, and Emergency Room (ER) Visits Per 30 Days Through Week 24 |
|---|---|

End point description:

Non-study medical visits were defined as the sum of primary care physician visits, nurse practitioner/physician's assistant/nurse visits, and medical or surgical specialist visits. Days hospitalized were defined as the sum of days in the general ward and days in intensive care. The number of telephone consultations and ER visits was assessed via individual questions on the electronic Case Report Form. The endpoint was totaled through Week 24, divided by the number of days on treatment for each participant, then multiplied by 30 days to get the number of visits per 30 days.

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

End point timeframe:

From Day 1 up to Week 24

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 429 | 432 | | |
| Units: events per 30 days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Non-Study Medical Visits | 0.726 (± 1.472) | 0.779 (± 1.690) | | |
| Telephone Consultations | 0.279 (± 0.718) | 0.312 (± 0.656) | | |

| | | | | |
|---|---|---|---|---|
| Hospital Days | 0.402 (± 2.273) | 0.562 (± 2.187) | | |
| ER Visits | 0.037 (± 0.156) | 0.067 (± 0.195) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Number of Laboratory Visits, Radiology Visits, Home Healthcare Visits, and Medical Procedures at Day 28 of Cycles 1-4

| | |
|---|---|
| End point title | Mean Number of Laboratory Visits, Radiology Visits, Home Healthcare Visits, and Medical Procedures at Day 28 of Cycles 1-4 |

End point description:

The number of non-study laboratory visits (NSLVs), non-study radiology visits (NSRVs), and home healthcare visits (HHVs) were each collected as a single question on the eCRF. The number of non-study medical or surgical procedures (MSPs) was defined as the sum of procedures performed at outpatient or physician clinics, as well as those performed during any inpatient hospitalization.

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

End point timeframe:

Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

| End point values | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 429 | 432 | | |
| Units: visits | | | | |
| arithmetic mean (standard deviation) | | | | |
| NSLV, Cycle 1 (n=417,414) | 0.3 (± 1.25) | 0.3 (± 1.14) | | |
| NSLV, Cycle 2 (n=345,363) | 0.3 (± 0.97) | 0.4 (± 1.35) | | |
| NSLV, Cycle 3 (n=299,304) | 0.2 (± 0.67) | 0.2 (± 0.58) | | |
| NSLV, Cycle 4 (n=265,254) | 0.1 (± 0.49) | 0.1 (± 0.47) | | |
| NSRV, Cycle 1 (n=419,414) | 0.1 (± 0.44) | 0.1 (± 0.56) | | |
| NSRV, Cycle 2 (n=348,364) | 0.1 (± 0.36) | 0.1 (± 0.88) | | |
| NSRV, Cycle 3 (n=299,305) | 0.0 (± 0.28) | 0.1 (± 0.33) | | |
| NSRV, Cycle 4 (n=266,255) | 0.0 (± 0.24) | 0.1 (± 0.46) | | |
| HHV, Cycle 1 (n=418,411) | 0.0 (± 0.44) | 0.1 (± 0.77) | | |
| HHV, Cycle 2 (n=343,363) | 0.1 (± 0.52) | 0.1 (± 0.64) | | |
| HHV, Cycle 3 (n=298,304) | 0.1 (± 0.72) | 0.0 (± 0.37) | | |
| HHV, Cycle 4 (n=265,254) | 0.0 (± 0.49) | 0.1 (± 1.77) | | |
| NSP, Cycle 1 (n=417,413) | 0.2 (± 0.69) | 0.3 (± 2.52) | | |
| NSP, Cycle 2 (n=344,363) | 0.2 (± 0.68) | 0.2 (± 1.17) | | |
| NSP, Cycle 3 (n=298,304) | 0.2 (± 0.60) | 0.3 (± 1.98) | | |
| NSP, Cycle 4 (n=266,254) | 0.2 (± 0.85) | 0.3 (± 1.73) | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: All collected deaths

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

End point description:

Pre-treatment deaths were collected from day of participant's informed consent to the day before first dose of study medication.
On-treatment deaths were collected from first dose of study medication to 28 days after last dose of study medication (on-treatment), up to approximately 129 months.
Deaths were collected in the post treatment survival follow up from 29 days after last dose of study medication until the end of the study, up to approximately 152 months.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Pre-treatment deaths: Up to 21 days prior to treatment. On-treatment deaths: Up to 129 months. Post-treatment deaths: up to 152 months.

| **End point values** | Pazopanib 800 mg | Sunitinib 50 mg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 557 | 553 | | |
| Units: Participants | | | | |
| Pre-treatment deaths | 0 | 0 | | |
| On-treatment deaths | 25 | 22 | | |
| Post-treatment deaths | 310 | 312 | | |
| All deaths | 335 | 334 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from first dose of study medication until the last dose plus 28 days post-treat follow-up, assessed up to approximately 129 months.

Adverse event reporting additional description:

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

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Pazopanib |

Reporting group description:

Pazopanib

| | |
|---|---|
| Reporting group title | Total |

Reporting group description:

Total

| | |
|---|---|
| Reporting group title | Sunitinib |

Reporting group description:

Sunitinib

| Serious adverse events | Pazopanib | Total | Sunitinib |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 242 / 554 (43.68%) | 469 / 1102 (42.56%) | 227 / 548 (41.42%) |
| number of deaths (all causes) | 335 | 669 | 334 |
| number of deaths resulting from adverse events | 3 | 11 | 8 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lipoma | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Haemangioblastoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endometrial cancer metastatic | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Cholesteatoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Cancer pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Malignant melanoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastasis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Paraneoplastic syndrome | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parathyroid tumour benign | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal cancer metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Signet-ring cell carcinoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour associated fever | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Tumour rupture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic thrombosis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial rupture | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dry gangrene | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Giant cell arteritis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 13 / 1102 (1.18%) | 6 / 548 (1.09%) |
| occurrences causally related to treatment / all | 5 / 7 | 9 / 13 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 18 / 1102 (1.63%) | 13 / 548 (2.37%) |
| occurrences causally related to treatment / all | 3 / 5 | 10 / 18 | 7 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 4 / 1102 (0.36%) | 3 / 548 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| General physical health deterioration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 15 / 1102 (1.36%) | 12 / 548 (2.19%) |
| occurrences causally related to treatment / all | 3 / 3 | 14 / 16 | 11 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Asthenia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 6 / 1102 (0.54%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 6 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| Penile oedema | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Bartholin's cyst | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 5 / 1102 (0.45%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 5 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 6 / 1102 (0.54%) | 6 / 548 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 6 | 4 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 13 / 1102 (1.18%) | 8 / 548 (1.46%) |
| occurrences causally related to treatment / all | 1 / 5 | 4 / 14 | 3 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |

| | | | |
|---|---|---|---|
| Laryngeal haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 12 / 1102 (1.09%) | 11 / 548 (2.01%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 14 | 2 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Pneumonitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 8 / 554 (1.44%) | 15 / 1102 (1.36%) | 7 / 548 (1.28%) |
| occurrences causally related to treatment / all | 5 / 8 | 9 / 15 | 4 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary pain | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Psychiatric disorders** | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mental status changes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Emotional distress | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 35 / 554 (6.32%) | 43 / 1102 (3.90%) | 8 / 548 (1.46%) |
| occurrences causally related to treatment / all | 36 / 37 | 42 / 45 | 6 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 17 / 554 (3.07%) | 19 / 1102 (1.72%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 16 / 17 | 18 / 19 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood calcium increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatine increased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Blood glucose decreased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood potassium increased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 9 / 1102 (0.82%) | 9 / 548 (1.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 8 / 9 | 8 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test increased | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 11 / 1102 (1.00%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 6 / 7 | 10 / 11 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 6 / 554 (1.08%) | 7 / 1102 (0.64%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 6 / 6 | 7 / 7 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 3 / 1102 (0.27%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Craniocerebral injury | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Contusion | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Ilium fracture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Brain herniation | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Ankle fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetabulum fracture | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Chemical poisoning | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple fractures | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Patella fracture | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Cardiac disorders | | | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Cardiopulmonary failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 5 / 1102 (0.45%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 5 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Acute myocardial infarction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 554 (0.54%) | 5 / 1102 (0.45%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 2 / 3 | 3 / 5 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Palpitations | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 7 / 1102 (0.64%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 2 / 3 | 6 / 7 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Torsade de pointes | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Nervous system disorders | | | |
| Central nervous system haemorrhage | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic cerebral infarction | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular insufficiency | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral small vessel ischaemic disease | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 6 / 1102 (0.54%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 3 / 5 | 4 / 6 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemianaesthesia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 5 / 1102 (0.45%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 5 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 554 (0.72%) | 7 / 1102 (0.64%) | 3 / 548 (0.55%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 7 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 5 / 1102 (0.45%) | 3 / 548 (0.55%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 5 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lethargy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 4 / 1102 (0.36%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 2 / 3 | 3 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microangiopathic haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 9 / 554 (1.62%) | 18 / 1102 (1.63%) | 9 / 548 (1.64%) |
| occurrences causally related to treatment / all | 6 / 9 | 13 / 18 | 7 / 9 |
| deaths causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 554 (0.72%) | 28 / 1102 (2.54%) | 24 / 548 (4.38%) |
| occurrences causally related to treatment / all | 4 / 4 | 29 / 29 | 25 / 25 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polycythaemia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 9 / 1102 (0.82%) | 7 / 548 (1.28%) |
| occurrences causally related to treatment / all | 2 / 2 | 8 / 9 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 8 / 1102 (0.73%) | 5 / 548 (0.91%) |
| occurrences causally related to treatment / all | 1 / 3 | 4 / 8 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal fistula | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Anal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric fistula | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 4 / 1102 (0.36%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 15 / 1102 (1.36%) | 10 / 548 (1.82%) |
| occurrences causally related to treatment / all | 5 / 5 | 14 / 16 | 9 / 11 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erosive oesophagitis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 3 / 1102 (0.27%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Swollen tongue | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 7 / 1102 (0.64%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 5 / 6 | 7 / 8 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis ulcerative | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 6 / 554 (1.08%) | 13 / 1102 (1.18%) | 7 / 548 (1.28%) |
| occurrences causally related to treatment / all | 5 / 6 | 11 / 13 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peptic ulcer | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 15 / 1102 (1.36%) | 8 / 548 (1.46%) |
| occurrences causally related to treatment / all | 3 / 7 | 10 / 16 | 7 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Jaundice cholestatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 8 / 554 (1.44%) | 8 / 1102 (0.73%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 8 / 8 | 8 / 8 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 11 / 1102 (1.00%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 7 / 7 | 11 / 11 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder rupture | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Renal and urinary disorders** | | | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |

| | | | |
|---|---|---|---|
| Renal impairment | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal haemorrhage | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 5 / 1102 (0.45%) | 4 / 548 (0.73%) |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 5 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 5 / 1102 (0.45%) | 3 / 548 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 6 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 554 (0.72%) | 13 / 1102 (1.18%) | 9 / 548 (1.64%) |
| occurrences causally related to treatment / all | 2 / 4 | 7 / 13 | 5 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc compression | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin pain | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Flank pain | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 3 / 1102 (0.27%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bone pain | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Back pain | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 8 / 1102 (0.73%) | 5 / 548 (0.91%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 8 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Osteolysis | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 2 / 1102 (0.18%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complicated appendicitis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile infection | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 2 / 1102 (0.18%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Perinephric abscess | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 4 / 1102 (0.36%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 3 / 554 (0.54%) | 4 / 1102 (0.36%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| Salmonella sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal abscess | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal abscess | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 13 / 1102 (1.18%) | 6 / 548 (1.09%) |
| occurrences causally related to treatment / all | 1 / 7 | 2 / 14 | 1 / 7 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 2 / 1102 (0.18%) | 0 / 548 (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 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 3 / 1102 (0.27%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 6 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperlipasaemia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 5 / 554 (0.90%) | 6 / 1102 (0.54%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 9 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 554 (0.18%) | 1 / 1102 (0.09%) | 0 / 548 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 8 / 554 (1.44%) | 19 / 1102 (1.72%) | 11 / 548 (2.01%) |
| occurrences causally related to treatment / all | 4 / 8 | 15 / 21 | 11 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 554 (0.36%) | 4 / 1102 (0.36%) | 2 / 548 (0.36%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 554 (0.72%) | 11 / 1102 (1.00%) | 7 / 548 (1.28%) |
| occurrences causally related to treatment / all | 1 / 4 | 6 / 11 | 5 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophosphataemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 554 (0.00%) | 1 / 1102 (0.09%) | 1 / 548 (0.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| 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** | Pazopanib | Total | Sunitinib |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 541 / 554 (97.65%) | 1076 / 1102 (97.64%) | 535 / 548 (97.63%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 256 / 554 (46.21%) | 476 / 1102 (43.19%) | 220 / 548 (40.15%) |
| occurrences (all) | 314 | 605 | 291 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 47 / 554 (8.48%) | 124 / 1102 (11.25%) | 77 / 548 (14.05%) |
| occurrences (all) | 58 | 165 | 107 |
| Oedema peripheral | | | |
| subjects affected / exposed | 58 / 554 (10.47%) | 144 / 1102 (13.07%) | 86 / 548 (15.69%) |
| occurrences (all) | 71 | 194 | 123 |
| Oedema | | | |
| subjects affected / exposed | 15 / 554 (2.71%) | 52 / 1102 (4.72%) | 37 / 548 (6.75%) |
| occurrences (all) | 16 | 61 | 45 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 62 / 554 (11.19%) | 203 / 1102 (18.42%) | 141 / 548 (25.73%) |
| occurrences (all) | 73 | 322 | 249 |
| Fatigue | | | |
| subjects affected / exposed | 305 / 554 (55.05%) | 647 / 1102 (58.71%) | 342 / 548 (62.41%) |
| occurrences (all) | 392 | 1041 | 649 |
| Face oedema | | | |
| subjects affected / exposed | 12 / 554 (2.17%) | 52 / 1102 (4.72%) | 40 / 548 (7.30%) |
| occurrences (all) | 12 | 79 | 67 |
| Chills | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 554 (2.71%) | 58 / 1102 (5.26%) | 43 / 548 (7.85%) |
| occurrences (all) | 15 | 66 | 51 |
| Asthenia | | | |
| subjects affected / exposed | 47 / 554 (8.48%) | 105 / 1102 (9.53%) | 58 / 548 (10.58%) |
| occurrences (all) | 91 | 195 | 104 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 86 / 554 (15.52%) | 191 / 1102 (17.33%) | 105 / 548 (19.16%) |
| occurrences (all) | 113 | 241 | 128 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 39 / 554 (7.04%) | 93 / 1102 (8.44%) | 54 / 548 (9.85%) |
| occurrences (all) | 41 | 108 | 67 |
| Epistaxis | | | |
| subjects affected / exposed | 49 / 554 (8.84%) | 145 / 1102 (13.16%) | 96 / 548 (17.52%) |
| occurrences (all) | 65 | 220 | 155 |
| Dyspnoea | | | |
| subjects affected / exposed | 79 / 554 (14.26%) | 171 / 1102 (15.52%) | 92 / 548 (16.79%) |
| occurrences (all) | 95 | 202 | 107 |
| Dysphonia | | | |
| subjects affected / exposed | 42 / 554 (7.58%) | 54 / 1102 (4.90%) | 12 / 548 (2.19%) |
| occurrences (all) | 47 | 59 | 12 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 58 / 554 (10.47%) | 119 / 1102 (10.80%) | 61 / 548 (11.13%) |
| occurrences (all) | 59 | 122 | 63 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 143 / 554 (25.81%) | 236 / 1102 (21.42%) | 93 / 548 (16.97%) |
| occurrences (all) | 176 | 310 | 134 |
| Amylase increased | | | |
| subjects affected / exposed | 39 / 554 (7.04%) | 63 / 1102 (5.72%) | 24 / 548 (4.38%) |
| occurrences (all) | 54 | 102 | 48 |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 128 / 554 (23.10%) | 224 / 1102 (20.33%) | 96 / 548 (17.52%) |
| occurrences (all) | 164 | 338 | 174 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 40 / 554 (7.22%) | 70 / 1102 (6.35%) | 30 / 548 (5.47%) |
| occurrences (all) | 41 | 87 | 46 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 51 / 554 (9.21%) | 86 / 1102 (7.80%) | 35 / 548 (6.39%) |
| occurrences (all) | 82 | 153 | 71 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 52 / 554 (9.39%) | 137 / 1102 (12.43%) | 85 / 548 (15.51%) |
| occurrences (all) | 98 | 300 | 202 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 40 / 554 (7.22%) | 100 / 1102 (9.07%) | 60 / 548 (10.95%) |
| occurrences (all) | 64 | 243 | 179 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 33 / 554 (5.96%) | 97 / 1102 (8.80%) | 64 / 548 (11.68%) |
| occurrences (all) | 45 | 162 | 117 |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 21 / 554 (3.79%) | 56 / 1102 (5.08%) | 35 / 548 (6.39%) |
| occurrences (all) | 42 | 103 | 61 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 34 / 554 (6.14%) | 109 / 1102 (9.89%) | 75 / 548 (13.69%) |
| occurrences (all) | 47 | 237 | 190 |
| Lipase increased | | | |
| subjects affected / exposed | 43 / 554 (7.76%) | 75 / 1102 (6.81%) | 32 / 548 (5.84%) |
| occurrences (all) | 66 | 119 | 53 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 23 / 554 (4.15%) | 83 / 1102 (7.53%) | 60 / 548 (10.95%) |
| occurrences (all) | 48 | 192 | 144 |
| Platelet count decreased | | | |
| subjects affected / exposed | 36 / 554 (6.50%) | 133 / 1102 (12.07%) | 97 / 548 (17.70%) |
| occurrences (all) | 68 | 330 | 262 |
| Weight decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 86 / 554 (15.52%) | 119 / 1102 (10.80%) | 33 / 548 (6.02%) |
| occurrences (all) | 99 | 134 | 35 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 31 / 554 (5.60%) | 105 / 1102 (9.53%) | 74 / 548 (13.50%) |
| occurrences (all) | 55 | 223 | 168 |
| Nervous system disorders | | | |
| Taste disorder | | | |
| subjects affected / exposed | 99 / 554 (17.87%) | 244 / 1102 (22.14%) | 145 / 548 (26.46%) |
| occurrences (all) | 106 | 368 | 262 |
| Headache | | | |
| subjects affected / exposed | 124 / 554 (22.38%) | 246 / 1102 (22.32%) | 122 / 548 (22.26%) |
| occurrences (all) | 159 | 338 | 179 |
| Dysgeusia | | | |
| subjects affected / exposed | 49 / 554 (8.84%) | 107 / 1102 (9.71%) | 58 / 548 (10.58%) |
| occurrences (all) | 58 | 136 | 78 |
| Dizziness | | | |
| subjects affected / exposed | 71 / 554 (12.82%) | 153 / 1102 (13.88%) | 82 / 548 (14.96%) |
| occurrences (all) | 87 | 192 | 105 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 51 / 554 (9.21%) | 151 / 1102 (13.70%) | 100 / 548 (18.25%) |
| occurrences (all) | 114 | 364 | 250 |
| Neutropenia | | | |
| subjects affected / exposed | 60 / 554 (10.83%) | 207 / 1102 (18.78%) | 147 / 548 (26.82%) |
| occurrences (all) | 121 | 504 | 383 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 56 / 554 (10.11%) | 236 / 1102 (21.42%) | 180 / 548 (32.85%) |
| occurrences (all) | 118 | 614 | 496 |
| Anaemia | | | |
| subjects affected / exposed | 36 / 554 (6.50%) | 135 / 1102 (12.25%) | 99 / 548 (18.07%) |
| occurrences (all) | 49 | 209 | 160 |
| Eye disorders | | | |
| Eyelid oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 18 / 554 (3.25%) | 57 / 1102 (5.17%) | 39 / 548 (7.12%) |
| occurrences (all) | 32 | 124 | 92 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 24 / 554 (4.33%) | 57 / 1102 (5.17%) | 33 / 548 (6.02%) |
| occurrences (all) | 32 | 70 | 38 |
| Abdominal distension | | | |
| subjects affected / exposed | 34 / 554 (6.14%) | 61 / 1102 (5.54%) | 27 / 548 (4.93%) |
| occurrences (all) | 35 | 67 | 32 |
| Abdominal pain | | | |
| subjects affected / exposed | 72 / 554 (13.00%) | 146 / 1102 (13.25%) | 74 / 548 (13.50%) |
| occurrences (all) | 86 | 194 | 108 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 69 / 554 (12.45%) | 118 / 1102 (10.71%) | 49 / 548 (8.94%) |
| occurrences (all) | 89 | 152 | 63 |
| Constipation | | | |
| subjects affected / exposed | 97 / 554 (17.51%) | 230 / 1102 (20.87%) | 133 / 548 (24.27%) |
| occurrences (all) | 112 | 301 | 189 |
| Diarrhoea | | | |
| subjects affected / exposed | 349 / 554 (63.00%) | 661 / 1102 (59.98%) | 312 / 548 (56.93%) |
| occurrences (all) | 752 | 1616 | 864 |
| Dyspepsia | | | |
| subjects affected / exposed | 78 / 554 (14.08%) | 213 / 1102 (19.33%) | 135 / 548 (24.64%) |
| occurrences (all) | 93 | 302 | 209 |
| Dry mouth | | | |
| subjects affected / exposed | 26 / 554 (4.69%) | 55 / 1102 (4.99%) | 29 / 548 (5.29%) |
| occurrences (all) | 29 | 61 | 32 |
| Vomiting | | | |
| subjects affected / exposed | 158 / 554 (28.52%) | 306 / 1102 (27.77%) | 148 / 548 (27.01%) |
| occurrences (all) | 303 | 629 | 326 |
| Stomatitis | | | |
| subjects affected / exposed | 78 / 554 (14.08%) | 232 / 1102 (21.05%) | 154 / 548 (28.10%) |
| occurrences (all) | 99 | 402 | 303 |
| Oral pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 554 (2.17%) | 40 / 1102 (3.63%) | 28 / 548 (5.11%) |
| occurrences (all) | 14 | 58 | 44 |
| Nausea | | | |
| subjects affected / exposed | 248 / 554 (44.77%) | 501 / 1102 (45.46%) | 253 / 548 (46.17%) |
| occurrences (all) | 399 | 879 | 480 |
| Mouth ulceration | | | |
| subjects affected / exposed | 22 / 554 (3.97%) | 57 / 1102 (5.17%) | 35 / 548 (6.39%) |
| occurrences (all) | 28 | 80 | 52 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 19 / 554 (3.43%) | 74 / 1102 (6.72%) | 55 / 548 (10.04%) |
| occurrences (all) | 19 | 88 | 69 |
| Flatulence | | | |
| subjects affected / exposed | 32 / 554 (5.78%) | 47 / 1102 (4.26%) | 15 / 548 (2.74%) |
| occurrences (all) | 37 | 57 | 20 |
| Skin and subcutaneous tissue disorders | | | |
| Yellow skin | | | |
| subjects affected / exposed | 4 / 554 (0.72%) | 97 / 1102 (8.80%) | 93 / 548 (16.97%) |
| occurrences (all) | 5 | 156 | 151 |
| Pruritus | | | |
| subjects affected / exposed | 23 / 554 (4.15%) | 68 / 1102 (6.17%) | 45 / 548 (8.21%) |
| occurrences (all) | 29 | 86 | 57 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 163 / 554 (29.42%) | 438 / 1102 (39.75%) | 275 / 548 (50.18%) |
| occurrences (all) | 248 | 863 | 615 |
| Hair colour changes | | | |
| subjects affected / exposed | 168 / 554 (30.32%) | 222 / 1102 (20.15%) | 54 / 548 (9.85%) |
| occurrences (all) | 178 | 237 | 59 |
| Dry skin | | | |
| subjects affected / exposed | 44 / 554 (7.94%) | 91 / 1102 (8.26%) | 47 / 548 (8.58%) |
| occurrences (all) | 53 | 106 | 53 |
| Alopecia | | | |
| subjects affected / exposed | 77 / 554 (13.90%) | 122 / 1102 (11.07%) | 45 / 548 (8.21%) |
| occurrences (all) | 83 | 129 | 46 |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 95 / 554 (17.15%) | 221 / 1102 (20.05%) | 126 / 548 (22.99%) |
| occurrences (all) | 143 | 344 | 201 |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 99 / 554 (17.87%) | 175 / 1102 (15.88%) | 76 / 548 (13.87%) |
| occurrences (all) | 148 | 301 | 153 |
| Haematuria | | | |
| subjects affected / exposed | 24 / 554 (4.33%) | 52 / 1102 (4.72%) | 28 / 548 (5.11%) |
| occurrences (all) | 29 | 70 | 41 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 7 / 554 (1.26%) | 36 / 1102 (3.27%) | 29 / 548 (5.29%) |
| occurrences (all) | 7 | 38 | 31 |
| Hypothyroidism | | | |
| subjects affected / exposed | 71 / 554 (12.82%) | 209 / 1102 (18.97%) | 138 / 548 (25.18%) |
| occurrences (all) | 74 | 247 | 173 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 70 / 554 (12.64%) | 163 / 1102 (14.79%) | 93 / 548 (16.97%) |
| occurrences (all) | 82 | 217 | 135 |
| Myalgia | | | |
| subjects affected / exposed | 34 / 554 (6.14%) | 71 / 1102 (6.44%) | 37 / 548 (6.75%) |
| occurrences (all) | 39 | 83 | 44 |
| Muscle spasms | | | |
| subjects affected / exposed | 38 / 554 (6.86%) | 61 / 1102 (5.54%) | 23 / 548 (4.20%) |
| occurrences (all) | 50 | 81 | 31 |
| Arthralgia | | | |
| subjects affected / exposed | 98 / 554 (17.69%) | 180 / 1102 (16.33%) | 82 / 548 (14.96%) |
| occurrences (all) | 133 | 249 | 116 |
| Back pain | | | |
| subjects affected / exposed | 91 / 554 (16.43%) | 180 / 1102 (16.33%) | 89 / 548 (16.24%) |
| occurrences (all) | 110 | 246 | 136 |
| Flank pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 14 / 554 (2.53%) | 44 / 1102 (3.99%) | 30 / 548 (5.47%) |
| occurrences (all) | 18 | 58 | 40 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 46 / 554 (8.30%) | 88 / 1102 (7.99%) | 42 / 548 (7.66%) |
| occurrences (all) | 77 | 142 | 65 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 30 / 554 (5.42%) | 64 / 1102 (5.81%) | 34 / 548 (6.20%) |
| occurrences (all) | 40 | 87 | 47 |
| Urinary tract infection | | | |
| subjects affected / exposed | 23 / 554 (4.15%) | 52 / 1102 (4.72%) | 29 / 548 (5.29%) |
| occurrences (all) | 32 | 72 | 40 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 207 / 554 (37.36%) | 410 / 1102 (37.21%) | 203 / 548 (37.04%) |
| occurrences (all) | 305 | 633 | 328 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 16 / 554 (2.89%) | 46 / 1102 (4.17%) | 30 / 548 (5.47%) |
| occurrences (all) | 24 | 64 | 40 |
| Hyponatraemia | | | |
| subjects affected / exposed | 22 / 554 (3.97%) | 58 / 1102 (5.26%) | 36 / 548 (6.57%) |
| occurrences (all) | 34 | 86 | 52 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 21 / 554 (3.79%) | 53 / 1102 (4.81%) | 32 / 548 (5.84%) |
| occurrences (all) | 35 | 92 | 57 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 27 October 2008 | Amendment 1: Country Specific Amendment for Japan to add pharmacokinetic sampling for subjects randomized to pazopanib |
| 01 April 2009 | Amendment 2: Updates to Inclusion/Exclusion criteria, dose modification guidelines for liver toxicity, concomitant medication, addition of pharmacogenetic sampling and Supplementary Quality of Life Questions. |
| 15 June 2009 | Amendment 3: Country Specific Amendment for China to permit using 12.5 mg capsules of sunitinib for 50 mg, 37.5 mg, and 25 mg dose levels. |
| 25 March 2011 | Amendment 4: Change to safety visit schedule to decrease number of visits after Cycle 9 from Day 28 and Day 42 per cycle, to Day 42 per cycle. Changes in Data Analysis section to sample size assumptions and inclusion of subjects from Study A2201 for the analysis of safety and efficacy. |
| 17 May 2013 | Amendment 5: Changes to allow subjects continued access to pazopanib or sunitinib therapy following the Treatment Phase (in the absence of unacceptable toxicity, disease progression, or subject withdrawal). Subject treatment and disease management was conducted as indicated by local standard of medical care. Subjects who had already discontinued study treatment and were in progressive disease follow-up or survival follow-up were considered as having completed the study.<br>Frequency of clinic visits reduced. Collection of safety information reduced to SAEs, pregnancies, AEs leading to study treatment discontinuation or other AEs the investigator deems important to report, and all other reasons leading to study treatment discontinuation. |
| 05 December 2017 | Amendment 6: Country specific amendment for China to permit use of pazopanib 200mg tablets (commercial supply) instead of 400mg tablets (clinical supply) in China. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

The full investigators lists and other Clinical Study Report appendices were not transferred over during the change in sponsorship from GlaxoSmithKline (GSK) to Novartis, the team could not confirm or quality control the investigator sites list.

Notes: