# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Capecitabine and Cisplatin With or Without Ramucirumab as First-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (RAINFALL)

## Summary

| | |
|---|---|
| EudraCT number | 2014-002240-40 |
| Trial protocol | HU DE FI NL IT ES PL BE GB CZ DK |
| Global end of trial date | 14 August 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 August 2021 |
| First version publication date | 15 August 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | I4T-MC-JVCU |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02314117 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Trial Number: 15372 |

Notes:

### Sponsors

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

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 14 August 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 August 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of ramucirumab, which is a targeted antibody, in combination with capecitabine and cisplatin compared to capecitabine and cisplatin alone in participants with stomach cancer.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 January 2015 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Puerto Rico: 2 |
| Country: Number of subjects enrolled | Argentina: 43 |
| Country: Number of subjects enrolled | Hungary: 31 |
| Country: Number of subjects enrolled | United States: 73 |
| Country: Number of subjects enrolled | Czechia: 19 |
| Country: Number of subjects enrolled | Japan: 60 |
| Country: Number of subjects enrolled | United Kingdom: 42 |
| Country: Number of subjects enrolled | Russian Federation: 50 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Finland: 8 |
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | Poland: 18 |
| Country: Number of subjects enrolled | Italy: 73 |
| Country: Number of subjects enrolled | Mexico: 52 |

| | |
|---|---|
| Country: Number of subjects enrolled | Israel: 23 |
| Country: Number of subjects enrolled | France: 40 |
| Country: Number of subjects enrolled | Germany: 33 |
| Worldwide total number of subjects | 645 |
| EEA total number of subjects | 284 |

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) | 405 |
| From 65 to 84 years | 238 |
| 85 years and over | 2 |

## Subject disposition

### Recruitment

Recruitment details:

No Text Available

### Pre-assignment

Screening details:

Completers are defined as participants who died or those who were alive and off treatment when the study completed.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ramucirumab + Cisplatin + Capecitabine |

Arm description:

8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m^2) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Ramucirumab |
| Investigational medicinal product code | |
| Other name | LY3009806,IMC-1121B,Cyramza |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

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

Dosage and administration details:

Administered orally

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

| | |
|---|---|
| Investigational medicinal product name | Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |

| | |
|---|---|
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

| **Arm title** | Placebo + Cisplatin + Capecitabine |
|---|---|

Arm description:

Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m^2 cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day 5-FU IV on days 1 to 5 of each 21-day cycle.

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

Dosage and administration details:

Administered orally

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

| | |
|---|---|
| Investigational medicinal product name | Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered IV

| **Number of subjects in period 1** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine |
|---|---|---|
| Started | 326 | 319 |
| Received at least one dose of study drug | 323 | 315 |
| Completed | 314 | 303 |
| Not completed | 12 | 16 |
| Consent withdrawn by subject | 3 | 2 |

| | | |
|---|---|---|
| Lost to follow-up | 9 | 14 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ramucirumab + Cisplatin + Capecitabine |
| Reporting group description: | |
| 8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m^2) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle. | |
| Reporting group title | Placebo + Cisplatin + Capecitabine |
| Reporting group description: | |
| Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m^2 cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day 5-FU IV on days 1 to 5 of each 21-day cycle. | |

| Reporting group values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | Total |
|---|---|---|---|
| Number of subjects | 326 | 319 | 645 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 58.9 | 60.1 | |
| standard deviation | ± 11.6 | ± 11.8 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 112 | 104 | 216 |
| Male | 214 | 215 | 429 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 67 | 62 | 129 |
| Not Hispanic or Latino | 227 | 245 | 472 |
| Unknown or Not Reported | 32 | 12 | 44 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 12 | 11 | 23 |
| Asian | 38 | 31 | 69 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 2 | 3 | 5 |
| White | 256 | 264 | 520 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 17 | 10 | 27 |
| Region of Enrollment<br>Units: Subjects | | | |
| Puerto Rico | 1 | 1 | 2 |
| Argentina | 21 | 22 | 43 |
| Hungary | 15 | 16 | 31 |

| | | | |
|---|---|---|---|
| United States | 42 | 31 | 73 |
| Czechia | 11 | 8 | 19 |
| Japan | 32 | 28 | 60 |
| United Kingdom | 20 | 22 | 42 |
| Russia | 25 | 25 | 50 |
| Spain | 10 | 13 | 23 |
| Canada | 10 | 6 | 16 |
| Netherlands | 4 | 7 | 11 |
| Belgium | 8 | 5 | 13 |
| Finland | 3 | 5 | 8 |
| Denmark | 12 | 3 | 15 |
| Poland | 8 | 10 | 18 |
| Italy | 28 | 45 | 73 |
| Mexico | 26 | 26 | 52 |
| Israel | 11 | 12 | 23 |
| France | 19 | 21 | 40 |
| Germany | 20 | 13 | 33 |

## End points

### End points reporting groups

| Reporting group title | Ramucirumab + Cisplatin + Capecitabine |
|---|---|

Reporting group description:

8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m^2) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.

| Reporting group title | Placebo + Cisplatin + Capecitabine |
|---|---|

Reporting group description:

Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m^2 cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day 5-FU IV on days 1 to 5 of each 21-day cycle.

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

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

End point description:

PFS time was measured from the date of randomization to the date of radiographic(rgr) documentation of progression(by RECIST v.1.1) or the date of death due to any cause, whichever was earlier.If a participant did not have a complete baseline tumor assessment,then the PFS time was censored at the randomization date.If a participant was not known to have died or have rgr documented progression as of the data cutoff date for the analysis, the PFS time was censored at the last adequate tumor assessment date. If death or progressive disease(PD) occurred after 2 or more consecutive missing rgr visits,censoring occurred at the date of the last rgr visit prior to the missed visits.If death or PD occurred after postdiscontinuation(pdis) systemic anticancer therapy,censoring occurred at the date of last rgr visit prior to the start of pdis systemic anticancer therapy. PD was defined according to RECIST v.1.1.

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

End point timeframe:

Randomization to Radiological Disease Progression or Death from Any Cause (Up to 26 Months)

Analysis Population: First 508 randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=87 and Placebo+Cisplatin+Capecitabine=62.

| **End point values** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 255 | 253 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.72 (5.45 to 6.51) | 5.39 (4.47 to 5.72) | | |

### Statistical analyses

| **Statistical analysis title** | Progression-free Survival (PFS) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.753 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.607 |
| upper limit | 0.935 |

## Secondary: Overall Survival (OS)

| End point title | Overall Survival (OS) |
|---|---|

End point description:

OS was time from the date of randomization to the date of death from any cause. If the participant was alive at the cutoff for analysis (or was lost to follow-up), OS data were censored for analysis on the last date the participant was known to be alive.

Analysis Population Description (APD): All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=87 and Placebo + Cisplatin + Capecitabine=88.

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

End point timeframe:

Randomization to Death from Any Cause (Up To 30 Months)

| **End point values** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.17 (9.92 to 11.93) | 10.74 (9.53 to 11.89) | | |

## Statistical analyses

| **Statistical analysis title** | Overall Survival (OS) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |

| | |
|---|---|
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.962 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.801 |
| upper limit | 1.156 |

## Secondary: Progression- free Survival 2 (PFS2)

| | |
|---|---|
| End point title | Progression- free Survival 2 (PFS2) |

End point description:

PFS2 was defined as the time from the date of randomization to second disease progression (defined as objective radiological or symptomatic progression), or death of any cause, whichever occurs first. Participants alive and for whom a second disease progression has not been observed (including participants who did not receive any additional
systemic anticancer treatments) were censored at the last time known to be alive and without second disease progression. The second progression refers to disease progression on or
after additional systemic anticancer therapy, regardless if any earlier progression is observed or not(e.g. at the end of study treatment). It is assessed by investigator based on overall clinical evaluation, not limited to RECIST.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=74 and Placebo + Cisplatin + Capecitabine=74.

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

End point timeframe:

Randomization to Second Radiological or Symptomatic Disease Progression After the Start of Additional Systemic Anticancer Treatment or Death from Any Cause (Up To 26 Months)

| **End point values** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.18 (9.03 to 10.84) | 9.20 (8.34 to 9.99) | | |

### Statistical analyses

| **Statistical analysis title** | Progression- free Survival 2 (PFS2) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |

| | |
|---|---|
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.926 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.774 |
| upper limit | 1.108 |

## Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR])

| | |
|---|---|
| End point title | Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR]) |

End point description:

Response was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.1).Target lesions - CR: Disappearance of all lesions; any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum. PD: At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Non target lesions – CR: Disappearance of all lesions and normalization of tumor marker levels; all lymph nodes must be non-pathological in size. Non-CR/Non-PD: Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels. PD: Unequivocal progression of existing lesions or the appearance of new lesion(s).ORR calculated as:(sum of the number of participants with PRs and CRs) divided by (number of evaluable participants) multiplied by 100.

APD: All randomized participants.

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

End point timeframe:

Randomization to Disease Progression (Up To 26 Months)

| **End point values** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 41.1 (35.8 to 46.4) | 36.4 (31.1 to 41.6) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants With Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control Rate [DCR])

| | |
|---|---|
| End point title | Percentage of Participants With Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control |

| | |
|---|---|
| | Rate [DCR]) |

End point description:

DCR was the percentage of participants with a best overall response of CR, PR, or SD as per Response using RECIST v1.1 criteria. Target lesions - CR: Disappearance of all lesions; any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum. Progressive Disease (PD): At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Non target lesions – CR: Disappearance of all lesions and normalization of tumor marker levels; all lymph nodes must be non-pathological in size. Non-CR/Non-PD: Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels. PD: Unequivocal progression of existing lesions or the appearance of new lesion(s).

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

End point timeframe:

Randomization to Disease Progression (Up To 26 Months)

APD: All randomized participants.

| **End point values** | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 81.9 (77.7 to 86.1) | 76.5 (71.8 to 81.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP)

| | |
|---|---|
| End point title | Time to Progression (TTP) |

End point description:

TTP was time from the date of randomization to the date of radiographic progression (according to RECIST v.1.1). If a participant died due to any reason without radiographic progression, TTP is censored at the last adequate tumor assessment. Target lesions: Progressive Disease (PD): At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Non target lesions: PD: Unequivocal progression of existing lesions or the appearance of new lesion(s).

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

End point timeframe:

Randomization to Disease Progression (Up To 24 Months)

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=149 and Placebo + Cisplatin + Capecitabine=111.

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.77 (5.88 to 7.66) | 5.78 (5.55 to 6.37) | | |

**Statistical analyses**

| Statistical analysis title | Time to Progression (TTP) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.699 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.569 |
| upper limit | 0.859 |

**Secondary: Duration of Response (DoR)**

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

End point description:

Participants achieved an objective response if they had a best overall response of CR or PR.Target lesions- CR:Disappearance of all lesions;any pathological lymph nodes must have reduction in short axis to <10 mm.PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum.PD: At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study(the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s).Non target lesions - CR: Disappearance of all lesions and normalization of tumour marker levels;all lymph nodes must be non-pathological in size. Non-CR/Non-PD:Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels.PD:Unequivocal progression of existing lesions or the appearance of new lesion(s).If a participant was not known to have died or have radiographically documented PD as of the data inclusion cutoff date,DOR was censored at the date of the last adequate tumor assessment.

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

End point timeframe:

Date of Complete Response (CR) or Partial Response (PR) to Date of Objective Disease Progression or Death Due to Any Cause (Up To 26 Months)

All randomized participants.Censored:Ramucirumab+Cisplatin+Capecitabine=23 & Placebo +Cisplatin+Capecitabine=10

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 134 | 116 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.72 (5.09 to 6.34) | 4.27 (3.88 to 4.90) | | |

**Statistical analyses**

| Statistical analysis title | Duration of Response (DoR) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.657 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.499 |
| upper limit | 0.866 |

**Secondary: Time to Deterioration in Quality of Life (QoL) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) - Global Health Status/ QoL Scale**

| End point title | Time to Deterioration in Quality of Life (QoL) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) - Global Health Status/ QoL Scale |
|---|---|

End point description:

Time to sustained deterioration was defined as time from randomization to first worsening in QoL with no subsequent non-worsened assessment. Worsening in global health status/QoL was defined as a decrease of ≥10 points on a 100-point scale. If a participant did not report worsening, time to sustained deterioration was censored at date of last non-worsened assessment.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=215 and Placebo + Cisplatin + Capecitabine=217.

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

End point timeframe:

Randomization, First worsening in QoL (Up To 26 Months)

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326 | 319 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.00 (8.08 to 12.58) | 9.46 (6.74 to 11.99) | | |

**Statistical analyses**

| Statistical analysis title | Time to Deterioration in Quality of Life (QoL) |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.013 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.332 |

## Secondary: Change in Health Status on the EuroQol 5-Dimensions 5-Level Instrument (EQ-5D- 5L)

| End point title | Change in Health Status on the EuroQol 5-Dimensions 5-Level Instrument (EQ-5D- 5L) |
|---|---|

End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status. Five dimensions of health status are each assessed with 5 response options and scored as a composite index which were anchored on a scale of 0 to 1 with a higher score representing better health status. Additionally, current health status was assessed on a visual analogue scale (VAS) ranging from 0 to 100 with a higher score representing better health status.

APD: All randomized participants who provided data at baseline and cycle 6.

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

End point timeframe:

Randomization, 30 Days After Treatment Discontinuation (Up To 5 Months)

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 136 | 125 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|---|---|---|---|---|
| EQ-5D index | -0.008 (± 0.148) | -0.010 (± 0.157) | | |
| EQ-5D VAS | 0.8 (± 18.56) | 1.5 (± 20.33) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

| End point title | Time to Deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) |
|---|---|

End point description:

The time from the date of randomization to the first date observing ECOG PS ≥2 (that is, deterioration from baseline status of 0 or 1). Participants without PS deterioration were censored at their last documented assessments of 0 or 1. ECOG Performance Status: 2- Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 -Completely disabled. Cannot carry on any selfcare.Totally confined to bed or chair,5- Dead.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=254 and Placebo + Cisplatin + Capecitabine= 260.

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

End point timeframe:

Randomization to ECOG PS ≥2 (Up To 26 Months)

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 326[1] | 319[2] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 999 (12.2 to 999) | 999 (999 to 999) | | |

Notes:

[1] - 999=NA.
Very few events occurred therefore data were not assessable.
[2] - 999=NA
Very few events occurred therefore data were not assessable.

### Statistical analyses

| Statistical analysis title | Time to Deterioration ECOG and PS |
|---|---|
| Comparison groups | Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine |
| Number of subjects included in analysis | 645 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.117 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.58 |

## Secondary: Number of Participants with Anti-Ramucirumab Antibodies

| End point title | Number of Participants with Anti-Ramucirumab Antibodies |
|---|---|

End point description:

Participants who developed treatment-emergent antibody responses to Ramucirumab postbaseline.

Analysis Population Description: All participants who received at least one dose of study drug.

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

End point timeframe:

Predose Cycle 1 through 30 Days After Treatment Discontinuation (Up To 24 Months)

| End point values | Ramucirumab + Cisplatin + Capecitabine | Placebo + Cisplatin + Capecitabine | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 323 | 315 | | |
| Units: participants | 4 | 5 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab

| End point title | Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab[3] |
|---|---|

End point description:

Pharmacokinetics (PK): Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab

APD: All randomized participants who received ramucirumab and had evaluable PK data.

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

End point timeframe:

Cycle 1 Day 1: 1 hour (hr) end of infusion (EOI), Cycle 3 Day 1: 1hr EOI, Cycle 9 Day 1: 1 hr EOI

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK analysis were only planned for experimental arm Ramucirumab + Cisplatin + Capecitabine.

| End point values | Ramucirumab + Cisplatin + Capecitabine | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 283 | | | |
| Units: Microgram/milliliter (µg/mL) | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Day 1 | 133 (± 31) | | | |
| Cycle 3, Day 1 | 173 (± 35) | | | |
| Cycle 9, Day 1 | 169 (± 60) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: PK: Minimum Concentration (Cmin) of Ramucirumab

| End point title | PK: Minimum Concentration (Cmin) of Ramucirumab[4] |
|---|---|

End point description:

Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

APD: All randomized participants who received ramucirumab and had evaluable PK data.

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

End point timeframe:

Cycle 1 Day 1: 1 hour (hr) end of infusion (EOI), Cycle 3 Day 1: 1hr EOI, Cycle 9 Day 1: 1 hr EOI

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analysis were only planned for experimental arm Ramucirumab + Cisplatin + Capecitabine.

| End point values | Ramucirumab + Cisplatin + Capecitabine | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 268 | | | |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cycle 1, Day 8 | 40.7 (± 35) | | | |
| Cycle 2, Day 1 | 35.7 (± 56) | | | |
| Cycle 3, Day 1 | 51.2 (± 47) | | | |
| Cycle 5, Day 1 | 69.7 (± 52) | | | |
| Cycle 9, Day 1 | 77.6 (± 98) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline Up to 5.6 Years

Adverse event reporting additional description:

All participants who received at least one dose of study drug.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo+Capecitabine+Cisplatin |

Reporting group description:

Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m^2 cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day 5-FU IV on days 1 to 5 of each 21-day cycle.

| | |
|---|---|
| Reporting group title | LY3009806+Capecitabine+Cisplatin |

Reporting group description:

8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m^2) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m^2 capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m^2/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.

| Serious adverse events | Placebo+Capecitabine+Cisplatin | LY3009806+Capecitabine+Cisplatin | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 150 / 315 (47.62%) | 161 / 323 (49.85%) | |
| number of deaths (all causes) | 21 | 19 | |
| number of deaths resulting from adverse events | 8 | 7 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| colorectal cancer | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| malignant pleural effusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| metastases to peritoneum | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tumour associated fever | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tumour haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| arterial thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| brachiocephalic vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| circulatory collapse | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deep vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 315 (0.95%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| embolism arterial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| embolism venous | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypertension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypotension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypovolaemic shock | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| orthostatic hypotension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| phlebitis deep | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subclavian vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombophlebitis superficial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| venous thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| venous thrombosis limb | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 3 / 323 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| complication associated with device | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| death | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| device occlusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fall | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| fatigue | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| general physical health deterioration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 315 (1.59%) | 6 / 323 (1.86%) | |
| occurrences causally related to treatment / all | 4 / 5 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| heparin-induced thrombocytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| impaired healing | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infusion related reaction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| malaise | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 3 / 323 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| mucosal inflammation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| multiple organ dysfunction syndrome | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 3 | 0 / 0 | |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyrexia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 12 / 315 (3.81%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 3 / 12 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sudden death | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Immune system disorders | | | |
| hypersensitivity | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| acute respiratory distress syndrome | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hiccups | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypoxia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lung disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pleural effusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia aspiration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumothorax | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |

| | | | |
|---|---|---|---|
| pneumothorax spontaneous | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pulmonary embolism | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 9 / 315 (2.86%) | 7 / 323 (2.17%) | |
| occurrences causally related to treatment / all | 7 / 9 | 5 / 7 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 1 | |
| respiratory failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| confusional state | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| delirium | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| depression | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| alanine aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| aspartate aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| blood bilirubin increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| blood creatinine increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| blood potassium decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| body temperature increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| creatinine renal clearance decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutrophil count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| platelet count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| weight decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| white blood cell count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| accidental overdose | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| device dislocation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 315 (0.95%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal stoma complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin laceration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vascular access complication | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| acute myocardial infarction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| angina pectoris | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| arrhythmia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| arrhythmia supraventricular | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| atrial fibrillation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| atrioventricular block complete | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cardiac arrest | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| cardiac disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| cardiogenic shock | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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|---|---|---|---|
| pericardial effusion | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sinus bradycardia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sinus node dysfunction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| supraventricular extrasystoles | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| tachycardia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Nervous system disorders** | | | |
| cerebral infarction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cerebrovascular accident | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 315 (0.95%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| cognitive disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dizziness | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemorrhage intracranial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ischaemic stroke | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nervous system disorder | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| presyncope | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| syncope | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 11 / 315 (3.49%) | 11 / 323 (3.41%) | |
| occurrences causally related to treatment / all | 13 / 16 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| blood loss anaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| bone marrow failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| febrile neutropenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 11 / 315 (3.49%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 12 / 13 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haemolytic anaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| leukopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 8 / 315 (2.54%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 9 / 9 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pancytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| thrombocytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| retinal vein thrombosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| abdominal distension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| abdominal pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 7 / 315 (2.22%) | 13 / 323 (4.02%) | |
| occurrences causally related to treatment / all | 0 / 10 | 3 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| abdominal pain upper | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| abdominal rigidity | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| acute abdomen | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ascites | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 3 / 323 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| colitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| constipation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 3 / 323 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| diarrhoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 19 / 315 (6.03%) | 11 / 323 (3.41%) | |
| occurrences causally related to treatment / all | 16 / 20 | 10 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dysphagia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 7 / 315 (2.22%) | 8 / 323 (2.48%) | |
| occurrences causally related to treatment / all | 0 / 8 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enteritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enterocolitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enterocutaneous fistula | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| erosive oesophagitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastric haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 315 (0.95%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| gastric perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 9 / 323 (2.79%) | |
| occurrences causally related to treatment / all | 1 / 1 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastric ulcer haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastric ulcer perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastrointestinal obstruction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| haematemesis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|---|
| haematochezia | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| hiatus hernia | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| ileus | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 2 / 323 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | | |
| ileus paralytic | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| impaired gastric emptying | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| inguinal hernia | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | | |
| intestinal obstruction | | | | |
| alternative dictionary used: MedDRA 23.0 | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 4 / 323 (1.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| intestinal perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| intra-abdominal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| large intestinal stenosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| large intestine perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lower gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| melaena | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| nausea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 8 / 315 (2.54%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 9 / 10 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| obstruction gastric | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oesophageal fistula | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oesophageal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| oesophageal stenosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumoperitoneum | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| rectal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| small intestinal obstruction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| small intestinal perforation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| stomatitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 4 / 323 (1.24%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| subileus | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 4 / 323 (1.24%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| upper gastrointestinal haemorrhage | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 3 / 323 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| vomiting | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 22 / 315 (6.98%) | 14 / 323 (4.33%) | |
| occurrences causally related to treatment / all | 20 / 27 | 9 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Hepatobiliary disorders | | | |
| bile duct obstruction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cholangitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hepatic failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| hyperbilirubinaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| dermatomyositis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| palmar-plantar erythrodysaesthesia syndrome | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| skin disorder | | | |

| | | | |
|---|---|---|---|
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| acute kidney injury | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 8 / 315 (2.54%) | 10 / 323 (3.10%) | |
| occurrences causally related to treatment / all | 10 / 13 | 8 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| hydronephrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nephritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| nephropathy | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| proteinuria | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyelocaliectasis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal colic | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal failure | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| renal impairment | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary retention | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| urinary tract obstruction | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| back pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| osteonecrosis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| biliary tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cellulitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| cystitis bacterial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| device related infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| device related sepsis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| enterocolitis infectious | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 2 / 323 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| periodontitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| periorbital infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| peritonitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 7 / 315 (2.22%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| pneumonia bacterial | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pseudomembranous colitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pseudomonas infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pyelonephritis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| sepsis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 5 / 315 (1.59%) | 4 / 323 (1.24%) | |
| occurrences causally related to treatment / all | 3 / 5 | 2 / 5 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| septic shock | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| vascular device infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| cachexia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 0 / 315 (0.00%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| decreased appetite | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 3 / 315 (0.95%) | 5 / 323 (1.55%) | |
| occurrences causally related to treatment / all | 1 / 3 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| dehydration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 9 / 315 (2.86%) | 7 / 323 (2.17%) | |
| occurrences causally related to treatment / all | 4 / 9 | 4 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| hypercalcaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyperglycaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hyperkalaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypocalcaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypokalaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 4 / 315 (1.27%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypomagnesaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| hyponatraemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 2 / 315 (0.63%) | 6 / 323 (1.86%) | |
| occurrences causally related to treatment / all | 2 / 2 | 8 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| hypophosphataemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 0 / 323 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| malnutrition | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 1 / 315 (0.32%) | 1 / 323 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo+Capecitabine+Cisplatin | LY3009806+Capecitabine+Cisplatin | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 304 / 315 (96.51%) | 315 / 323 (97.52%) | |
| Vascular disorders | | | |
| embolism venous | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 17 / 315 (5.40%) | 13 / 323 (4.02%) | |
| occurrences (all) | 17 | 13 | |
| hypertension | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 23 / 315 (7.30%) | 70 / 323 (21.67%) | |
| occurrences (all) | 30 | 152 | |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 40 / 315 (12.70%) | 44 / 323 (13.62%) | |
| occurrences (all) | 101 | 133 | |
| fatigue | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 145 / 315 (46.03%) | 153 / 323 (47.37%) | |
| occurrences (all) | 309 | 316 | |
| mucosal inflammation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 17 / 315 (5.40%) | 20 / 323 (6.19%) | |
| occurrences (all) | 41 | 31 | |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 33 / 315 (10.48%) | 45 / 323 (13.93%) | |
| occurrences (all) | 46 | 65 | |
| pyrexia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 40 / 315 (12.70%) | 28 / 323 (8.67%) | |
| occurrences (all) | 56 | 37 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| cough | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 18 / 315 (5.71%) | 25 / 323 (7.74%) | |
| occurrences (all) | 18 | 29 | |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 21 / 315 (6.67%) | 36 / 323 (11.15%) | |
| occurrences (all) | 26 | 49 | |
| epistaxis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 14 / 315 (4.44%) | 48 / 323 (14.86%) | |
| occurrences (all) | 19 | 76 | |
| hiccups | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 33 / 315 (10.48%) | 36 / 323 (11.15%) | |
| occurrences (all) | 46 | 63 | |
| Psychiatric disorders | | | |
| insomnia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 25 / 315 (7.94%) | 27 / 323 (8.36%) | |
| occurrences (all) | 27 | 29 | |
| Investigations | | | |
| alanine aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 10 / 315 (3.17%) | 19 / 323 (5.88%) | |
| occurrences (all) | 15 | 29 | |
| aspartate aminotransferase increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 12 / 315 (3.81%) | 20 / 323 (6.19%) | |
| occurrences (all) | 17 | 25 | |
| blood creatinine increased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 28 / 315 (8.89%) | 31 / 323 (9.60%) | |
| occurrences (all) | 41 | 60 | |
| neutrophil count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 92 / 315 (29.21%) | 103 / 323 (31.89%) | |
| occurrences (all) | 263 | 295 | |
| platelet count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 33 / 315 (10.48%) | 72 / 323 (22.29%) | |
| occurrences (all) | 75 | 254 | |
| weight decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 37 / 315 (11.75%) | 54 / 323 (16.72%) | |
| occurrences (all) | 56 | 72 | |
| white blood cell count decreased | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 32 / 315 (10.16%) | 37 / 323 (11.46%) | |
| occurrences (all) | 109 | 118 | |
| Nervous system disorders | | | |
| dysgeusia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 27 / 315 (8.57%) | 34 / 323 (10.53%) | |
| occurrences (all) | 31 | 38 | |
| dizziness | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 35 / 315 (11.11%) | 36 / 323 (11.15%) | |
| occurrences (all) | 52 | 42 | |
| headache | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 27 / 315 (8.57%) | 43 / 323 (13.31%) | |
| occurrences (all) | 36 | 57 | |
| neuropathy peripheral | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 8 / 315 (2.54%) | 20 / 323 (6.19%) | |
| occurrences (all) | 9 | 30 | |
| peripheral sensory neuropathy | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 31 / 315 (9.84%) | 39 / 323 (12.07%) | |
| occurrences (all) | 41 | 62 | |
| Blood and lymphatic system disorders | | | |
| anaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 114 / 315 (36.19%) | 104 / 323 (32.20%) | |
| occurrences (all) | 289 | 276 | |
| neutropenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 74 / 315 (23.49%) | 71 / 323 (21.98%) | |
| occurrences (all) | 133 | 218 | |
| thrombocytopenia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 26 / 315 (8.25%) | 41 / 323 (12.69%) | |
| occurrences (all) | 51 | 106 | |
| Ear and labyrinth disorders | | | |
| tinnitus | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 27 / 315 (8.57%) | 23 / 323 (7.12%) | |
| occurrences (all) | 32 | 26 | |
| Gastrointestinal disorders | | | |
| abdominal pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 51 / 315 (16.19%) | 52 / 323 (16.10%) | |
| occurrences (all) | 69 | 80 | |
| abdominal pain upper | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 15 / 315 (4.76%) | 22 / 323 (6.81%) | |
| occurrences (all) | 22 | 27 | |
| constipation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 78 / 315 (24.76%) | 104 / 323 (32.20%) | |
| occurrences (all) | 107 | 161 | |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 107 / 315 (33.97%) | 108 / 323 (33.44%) | |
| occurrences (all) | 175 | 175 | |
| dyspepsia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 12 / 315 (3.81%) | 19 / 323 (5.88%) | |
| occurrences (all) | 14 | 20 | |
| dysphagia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 17 / 315 (5.40%) | 21 / 323 (6.50%) | |
| occurrences (all) | 23 | 33 | |
| nausea | | | |
| alternative dictionary used: MedDRA 23.0 | | | |

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|---|---|---|---|
| subjects affected / exposed | 186 / 315 (59.05%) | 205 / 323 (63.47%) | |
| occurrences (all) | 444 | 459 | |
| stomatitis | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 39 / 315 (12.38%) | 67 / 323 (20.74%) | |
| occurrences (all) | 64 | 110 | |
| vomiting | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 117 / 315 (37.14%) | 134 / 323 (41.49%) | |
| occurrences (all) | 217 | 249 | |
| Skin and subcutaneous tissue disorders | | | |
| alopecia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 16 / 315 (5.08%) | 19 / 323 (5.88%) | |
| occurrences (all) | 20 | 21 | |
| dry skin | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 16 / 315 (5.08%) | 20 / 323 (6.19%) | |
| occurrences (all) | 17 | 23 | |
| palmar-plantar erythrodysaesthesia syndrome | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 63 / 315 (20.00%) | 99 / 323 (30.65%) | |
| occurrences (all) | 121 | 248 | |
| skin hyperpigmentation | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 10 / 315 (3.17%) | 18 / 323 (5.57%) | |
| occurrences (all) | 10 | 18 | |
| Renal and urinary disorders | | | |
| proteinuria | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 36 / 315 (11.43%) | 64 / 323 (19.81%) | |
| occurrences (all) | 60 | 156 | |
| Musculoskeletal and connective tissue disorders | | | |

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|---|---|---|---|
| back pain | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 16 / 315 (5.08%) | 28 / 323 (8.67%) | |
| occurrences (all) | 20 | 33 | |
| Infections and infestations | | | |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 17 / 315 (5.40%) | 8 / 323 (2.48%) | |
| occurrences (all) | 18 | 11 | |
| Metabolism and nutrition disorders | | | |
| decreased appetite | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 100 / 315 (31.75%) | 130 / 323 (40.25%) | |
| occurrences (all) | 190 | 245 | |
| dehydration | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 25 / 315 (7.94%) | 19 / 323 (5.88%) | |
| occurrences (all) | 30 | 25 | |
| hypoalbuminaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 13 / 315 (4.13%) | 17 / 323 (5.26%) | |
| occurrences (all) | 21 | 28 | |
| hypocalcaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 11 / 315 (3.49%) | 20 / 323 (6.19%) | |
| occurrences (all) | 21 | 23 | |
| hypokalaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 40 / 315 (12.70%) | 36 / 323 (11.15%) | |
| occurrences (all) | 68 | 51 | |
| hypomagnesaemia | | | |
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 45 / 315 (14.29%) | 36 / 323 (11.15%) | |
| occurrences (all) | 97 | 47 | |
| hyponatraemia | | | |

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|---|---|---|---|
| alternative dictionary used: MedDRA 23.0 | | | |
| subjects affected / exposed | 17 / 315 (5.40%) | 18 / 323 (5.57%) | |
| occurrences (all) | 21 | 30 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported