



Clinical trial results:

Phase III study evaluating two strategies of maintenance, one with pemetrexed in continuous strategy and one according to the response of induction chemotherapy, in non squamous non small cell lung cancer of advanced stage

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-000092-16 |
| Trial protocol | FR |
| Global end of trial date | 30 November 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 15 December 2022 |
| First version publication date | 15 December 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | IFCT-GFPC-1101 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01631136 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | IFCT |
| Sponsor organisation address | 10 RUE DE LA GRANGE BATELIERE, PARIS, France, 75009 |
| Public contact | Contact, IFCT, 33 1568110545, contact@ifct.fr |
| Scientific contact | Contact, IFCT, 33 1568110545, contact@ifct.fr |

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 | 29 November 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Determinate in patients with metastatic non-squamous non small cell lung cancer without activating EGFR mutation or knowledge of ALK gene rearrangement the benefit in overall survival of a maintenance strategy determined by the response to induction chemotherapy by cisplatin-gemcitabine (continuation maintenance by gemcitabine for patient with objective response and switch maintenance by pemetrexed for patient with stable disease) compared to chemotherapy by cisplatin-pemetrexed followed by a continuation maintenance by pemetrexed.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 932 |
| Worldwide total number of subjects | 932 |
| EEA total number of subjects | 932 |

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) | 721 |
| From 65 to 84 years | 209 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

932 pts enrolled, 467 in the investigational arm and 465 in the reference arm. 1 patient excluded from analysis because no consent was found for him. The intent-to-treat (ITT) analysis thus deals with 931 pts. 257 patients received a maintenance in the experimental arm and 277 patients in the control arm.

Pre-assignment

Screening details:

Induction chemotherapy: Stage IV non-squamous NSCLC, Age 18-70 years, PS 0 or 1, adequate organ functions, No evidence of EGFR activating mutation or ALK rearrangement, Asymptomatic brain metastases, measurable disease (RECIST1.1). Maintenance: Objective Response (OR) or disease stabilization after induction, PS 0 or 1, Creatinine clearance >45 ml.

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Control Arm |

Arm description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

| | |
|--|----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion , Intravenous use |

Dosage and administration details:

Cisplatin 75 mg/m² at day 1 of each cycle. Control arm includes 4 induction cycles of 3 weeks. Cisplatin 1 mg/ml solution for infusion should be diluted before administration. The diluted solution should be administered by intravenous infusion only. When administering, avoid any device containing aluminium that may come into contact with cisplatin.

| | |
|--|-----------------------|
| Investigational medicinal product name | Pemetrexed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The dosage of pemetrexed is 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle. During induction chemotherapy, it is given in combination with cisplatin. Cisplatin should be administered 30 min after pemetrexed infusion. During maintenance period, pemetrexed is administered as monotherapy with the same dosage: 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle.

| | |
|------------------|---------------------|
| Arm title | Investigational Arm |
|------------------|---------------------|

Arm description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine

1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cisplatin 80 mg/m² at day 1 of each cycle. Investigationnal arm includes 4 induction cycles of 3 weeks in combination with gemcitabine.

CISPLATINE 1 mg/ml solution for infusion should be diluted before administration. The diluted solution should be administered by intravenous infusion only. When administering, avoid any device containing aluminium that may come into contact with cisplatin.

| | |
|--|----------------------------------|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

During induction, gemcitabine is given in combination with cisplatin at a dose of 1250mg/m² as a 30 minute intravenous infusion on Days 1 and day 8 followed by one week of rest for a 21 days cycle.

During maintenance, gemcitabine is given as monochemotherapy with the same dosage as induction.

| | |
|--|-----------------------|
| Investigational medicinal product name | Pemetrexed |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression. In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

The dosage of pemetrexed is 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle. During this maintenance period, pemetrexed is administrated as monotherapy with the same dosage as induction chemotherapy: 500 mg/m² body surface area as a 10-minute intravenous infusion on the first day of each 21-day cycle.

| Number of subjects in period 1^[1] | Control Arm | Investigational Arm |
|---|-------------|---------------------|
| Started | 465 | 466 |
| Completed | 0 | 0 |
| Not completed | 465 | 466 |
| Patient refusal | 15 | 15 |
| Physician decision | 6 | 14 |
| Adverse event, non-fatal | 77 | 68 |
| Death | 37 | 27 |

| | | |
|--|-----|-----|
| Intercurrent disease | 9 | 5 |
| Progression before study treatment beginning | 1 | 4 |
| Second cancer | - | 1 |
| Lack of efficacy | 316 | 326 |
| Protocol deviation | 4 | 6 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 932 patients were enrolled in the study. 467 in the investigational arm and 465 in the reference arm. One patient was not taken into consideration in the analysis because the patient's consent was lost. The inten-to-treat(ITT) analysis thus deals with 931 patients instead of 932.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Control Arm |
|-----------------------|-------------|

Reporting group description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

| | |
|-----------------------|---------------------|
| Reporting group title | Investigational Arm |
|-----------------------|---------------------|

Reporting group description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine 1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

| Reporting group values | Control Arm | Investigational Arm | Total |
|---|--------------|---------------------|-------|
| Number of subjects | 465 | 466 | 931 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 361 | 361 | 722 |
| From 65-84 years | 104 | 105 | 209 |
| 85 years and over | 0 | 0 | 0 |
| Adults (65-70 years) | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 60.1 | 59.2 | |
| full range (min-max) | 33.5 to 71.0 | 35.5 to 70.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 141 | 146 | 287 |
| Male | 324 | 320 | 644 |
| Performance status Units: Subjects | | | |
| PS 0 | 185 | 179 | 364 |
| PS 1 | 280 | 285 | 565 |
| PS 2 | 0 | 1 | 1 |
| Unknown | 0 | 1 | 1 |
| Smoking Units: Subjects | | | |

| | | | |
|------------------|-----|-----|-----|
| Smoker | 434 | 434 | 868 |
| Non smoker | 28 | 31 | 59 |
| Unknown | 3 | 1 | 4 |
| TNM | | | |
| Units: Subjects | | | |
| M1a | 87 | 95 | 182 |
| M1b | 378 | 371 | 749 |
| Brain metastasis | | | |
| Units: Subjects | | | |
| Yes | 109 | 88 | 197 |
| No | 356 | 378 | 734 |
| Histology | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 409 | 408 | 817 |
| Other | 56 | 58 | 114 |
| EGFR | | | |
| Units: Subjects | | | |
| Undetermined | 22 | 32 | 54 |
| Mutation | 8 | 9 | 17 |
| Not performed | 51 | 55 | 106 |
| Wild-type | 384 | 370 | 754 |

End points

End points reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Control Arm |
|-----------------------|-------------|

Reporting group description:

The control arm included 4 induction cycles with Cisplatin 75 mg/m² and Pemetrexed 500 mg/m² given every three weeks, followed by, in the absence of disease progression, a maintenance with Pemetrexed 500 mg/m² every 3 weeks, until progression or unacceptable toxicities. The second-line treatment was left to the investigator's choice.

| | |
|-----------------------|---------------------|
| Reporting group title | Investigational Arm |
|-----------------------|---------------------|

Reporting group description:

The investigational arm consist of a combination of Cisplatin 80 mg/m² every 3 weeks and Gemcitabine 1250 mg/m², on Day 1 and Day 8, every 3 weeks. After 4 cycles, the tumoral assessment by investigators determined the modalities for the maintenance treatment: in case of objective response (OR), continuation maintenance with Gemcitabine 1250 mg/m² given on Day 1 and Day 8 of 21-day cycles until progression or toxicity; in case of Stable Disease (SD), switch maintenance with Pemetrexed 500 mg/m² given every 3 weeks until progression (with folic acid and vitamin B12 supplementation). In case of maintenance with Gemcitabine, a second-line treatment with Pemetrexed was required until progression or toxicity.

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Intent-to-treat population |
|----------------------------|----------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

all patients who were enrolled in the study between july2012 and june 2016, with the exception of one patient for which no consent was found. He is excluded from this analysis. The intent-to-treat(ITT) analysis thus deals with 931 patients.

| | |
|----------------------------|---|
| Subject analysis set title | Intent-to-treat population -Control Arm |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Control ARM Intent-to-treat population : all patients randomised in control arm.

| | |
|----------------------------|--|
| Subject analysis set title | Intent-to-treat population - Investigational Arm |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

Intent-to-treat population - Investigational Arm: all patients randomized in investigational arm.

Primary: Overall Survival

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

End point description:

Overall survival is defined as the time from the date of randomisation until death due to any cause. It will be calculated using the Kaplan-Meier method. The comparison between the 2 arms will be performed using a two-sided Log-Rank test.

For patients who do not die, time to death will be censored at the time of last contact.

The analysis of the primary efficacy endpoint will be conducted in ITT population, based on overall survival.

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

End point timeframe:

Around 20 months

| End point values | Control Arm | Investigational Arm | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 465 | 466 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 10.38 (8.87 to 11.63) | 10.87 (9.56 to 12.09) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Overall survival |
| Comparison groups | Control Arm v Investigational Arm |
| Number of subjects included in analysis | 931 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.77 |
| Method | Logrank |

Secondary: Progression Free Survival

| | |
|------------------------|---|
| End point title | Progression Free Survival |
| End point description: | Progression-free survival is defined as the time from randomization to first observation of progression (according to RECIST v1.1) or date of death (from any cause). |
| End point type | Secondary |
| End point timeframe: | Around 5 months |

| End point values | Control Arm | Investigational Arm | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 465 | 466 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 4.53 (4.27 to 5.09) | 4.83 (4.5 to 5.09) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Progression Free Survival |
| Comparison groups | Control Arm v Investigational Arm |

| | |
|---|-------------------|
| Number of subjects included in analysis | 931 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.45 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.3 |
| upper limit | 5.1 |

Secondary: Control and response rate

| | |
|-------------------------------|---------------------------|
| End point title | Control and response rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| After 4 cycle study treatment | |

| End point values | Control Arm | Investigational Arm | | |
|-----------------------------|-----------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 465 | 466 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Objective response | 159 | 168 | | |
| Disease control | 355 | 330 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment exposure

| | |
|------------------------|--------------------|
| End point title | Treatment exposure |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| around 5 months | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety analysis was done on safety population comprising all patients who received at least one dose of induction therapy and assessed by number of patients with at least one adverse event in each arm.

Time Frame: Around 5 months

Adverse event reporting additional description:

Toxicity was assessed and graded using the NCICTC version 4.0.

The maximal grade of adverse events was collected by cycle of treatment.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Induction population _control arm |
|-----------------------|-----------------------------------|

Reporting group description:

Population including all patients who received at least one dose of induction chemotherapy (CP). The adverse events are reported from cycle1 day1 (C1D1) of induction chemotherapy until the day before the day 1 of maintenance chemotherapy.

| | |
|-----------------------|---|
| Reporting group title | Induction population _Investigational arm |
|-----------------------|---|

Reporting group description:

Population including all patients who received at least one dose of induction chemotherapy (CG). From cycle1 day1 (C1D1) of induction chemotherapy until the day before the day1 of maintenance chemotherapy.

| | |
|-----------------------|--|
| Reporting group title | Pemetrexed maintenance population _control arm |
|-----------------------|--|

Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with pemetrexed. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

| | |
|-----------------------|--|
| Reporting group title | Pemetrexed maintenance population _Investigational arm |
|-----------------------|--|

Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with pemetrexed in investigational arm. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

| | |
|-----------------------|--|
| Reporting group title | Gemcitabine maintenance population _Investigationalarm |
|-----------------------|--|

Reporting group description:

Population including all patients who received at least one dose of maintenance chemotherapy with gemcitabine in investigational arm. From cycle1 day1 (C1D1) of maintenance chemotherapy until the day before the day 1 of second line treatment therapy or 30 days after the last dose of maintenance therapy in case of the absence second line therapy.

| Serious adverse events | Induction population _control arm | Induction population _Investigational arm | Pemetrexed maintenance population _control arm |
|---|-----------------------------------|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 356 / 464 (76.72%) | 357 / 453 (78.81%) | 108 / 277 (38.99%) |
| number of deaths (all causes) | 367 | 361 | 25 |
| number of deaths resulting from | 67 | 56 | |

| | | | |
|---|------------------|------------------|-----------------|
| adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 5 / 453 (1.10%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Vascular disorders | | | |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 12 / 464 (2.59%) | 14 / 453 (3.09%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 0 / 12 | 1 / 15 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 7 / 464 (1.51%) | 6 / 453 (1.32%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 4 / 464 (0.86%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Microangiopathy | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Air embolism | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infarction | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arterial thrombosis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Varices oesophageal | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematoma | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| osteosynthesis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|------------------|------------------|
| General physical health deterioration | | | |
| subjects affected / exposed | 29 / 464 (6.25%) | 17 / 453 (3.75%) | 11 / 277 (3.97%) |
| occurrences causally related to treatment / all | 17 / 34 | 6 / 17 | 6 / 14 |
| deaths causally related to treatment / all | 0 / 8 | 0 / 6 | 0 / 6 |
| Asthenia | | | |
| subjects affected / exposed | 9 / 464 (1.94%) | 4 / 453 (0.88%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 5 / 9 | 3 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 464 (1.29%) | 8 / 453 (1.77%) | 5 / 277 (1.81%) |
| occurrences causally related to treatment / all | 1 / 7 | 2 / 9 | 2 / 5 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Chilitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Implant site dehiscence | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Injection site scar | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site thrombosis | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 7 / 464 (1.51%) | 7 / 453 (1.55%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 7 | 2 / 7 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 15 / 464 (3.23%) | 8 / 453 (1.77%) | 6 / 277 (2.17%) |
| occurrences causally related to treatment / all | 2 / 16 | 0 / 8 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 6 | 0 / 2 | 0 / 3 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 2 / 453 (0.44%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|------------------|-----------------|
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 3 / 453 (0.66%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 10 / 453 (2.21%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 2 / 4 | 6 / 10 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 6 / 464 (1.29%) | 12 / 453 (2.65%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 15 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 3 / 453 (0.66%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 3 / 453 (0.66%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Chylothorax | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |

| | | | |
|---|------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Suicidal behaviour | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychomotor retardation | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 464 (2.16%) | 10 / 453 (2.21%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 10 / 11 | 9 / 10 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 4 / 464 (0.86%) | 7 / 453 (1.55%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 4 / 4 | 7 / 7 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| White blood cell count increased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Splenic injury | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 4 / 453 (0.88%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 3 / 453 (0.66%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aphasia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paralysis recurrent laryngeal nerve | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clonus | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 4 / 453 (0.88%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 4 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Bone marrow failure | | | |
| subjects affected / exposed | 4 / 464 (0.86%) | 3 / 453 (0.66%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 3 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Neutrophil count decreased | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 464 (1.08%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 2 / 453 (0.44%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Eye disorder | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blindness unilateral | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|------------------|------------------|-----------------|
| Vomiting | | | |
| subjects affected / exposed | 8 / 464 (1.72%) | 14 / 453 (3.09%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 12 / 14 | 14 / 15 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 14 / 464 (3.02%) | 17 / 453 (3.75%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 17 / 18 | 17 / 18 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 5 / 453 (1.10%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 5 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 464 (1.51%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 8 / 8 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 2 / 453 (0.44%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Constipation | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 3 / 453 (0.66%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erythema | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin burning sensation | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 18 / 453 (3.97%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 3 / 3 | 17 / 19 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 6 / 464 (1.29%) | 10 / 453 (2.21%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6 | 9 / 10 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 4 / 453 (0.88%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 3 / 453 (0.66%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Polyarthritis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 4 / 464 (0.86%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 1 / 453 (0.22%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 8 / 464 (1.72%) | 6 / 453 (1.32%) | 3 / 277 (1.08%) |
| occurrences causally related to treatment / all | 4 / 8 | 4 / 6 | 3 / 5 |
| deaths causally related to treatment / all | 3 / 3 | 1 / 2 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| infectious colitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 2 / 453 (0.44%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Prostate infection | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arthritis infective | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital herpes | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 0 / 453 (0.00%) | 1 / 277 (0.36%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 464 (2.16%) | 1 / 453 (0.22%) | 2 / 277 (0.72%) |
| occurrences causally related to treatment / all | 8 / 11 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 4 / 464 (0.86%) | 4 / 453 (0.88%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 2 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 464 (0.00%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 3 / 464 (0.65%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acidosis | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 1 / 453 (0.22%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cachexia | | | |
| subjects affected / exposed | 1 / 464 (0.22%) | 0 / 453 (0.00%) | 0 / 277 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |

| Serious adverse events | Pemetrexed maintenance population _Investigational arm | Gemcitabine maintenance population _Investigationalarm | |
|---|---|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 40 / 115 (34.78%) | 80 / 142 (56.34%) | |
| number of deaths (all causes) | 10 | 18 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Phlebitis superficial | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microangiopathy | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Air embolism | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infarction | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arterial thrombosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varices oesophageal | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery thrombosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| osteosynthesis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 7 / 142 (4.93%) | |
| occurrences causally related to treatment / all | 1 / 2 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 4 | |

| | | | |
|---|-----------------|-----------------|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chilitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Implant site dehiscence | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection site scar | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site thrombosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 115 (3.48%) | 9 / 142 (6.34%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oropharyngeal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 4 / 142 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chylothorax | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary congestion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal behaviour | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychomotor retardation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Gastrointestinal stoma complication | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenic injury | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation necrosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Haemorrhagic stroke | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paralysis recurrent laryngeal nerve | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clonus | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blindness unilateral | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Nausea | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin burning sensation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 3 / 142 (2.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombotic microangiopathy | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarthritis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| infectious colitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis infective | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 1 / 142 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 2 / 142 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatitis E | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 115 (0.87%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital herpes | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | 0 / 142 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Induction population _control arm | Induction population _Investigational arm | Pemetrexed maintenance population _control arm |
|---|--------------------------------------|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 446 / 464 (96.12%) | 444 / 453 (98.01%) | 263 / 277 (94.95%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 7 / 464 (1.51%) | 8 / 453 (1.77%) | 18 / 277 (6.50%) |
| occurrences (all) | 0 | 0 | 8 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 192 / 464 (41.38%) | 228 / 453 (50.33%) | 124 / 277 (44.77%) |
| occurrences (all) | 193 | 228 | 215 |

| | | | |
|---|--|-------------------|-------------------|
| Pyrexia | | | |
| subjects affected / exposed | 30 / 464 (6.47%) | 40 / 453 (8.83%) | 23 / 277 (8.30%) |
| occurrences (all) | 30 | 42 | 26 |
| Chest pain | | | |
| subjects affected / exposed | 37 / 464 (7.97%) | 40 / 453 (8.83%) | 27 / 277 (9.75%) |
| occurrences (all) | 30 | 42 | 38 |
| Oedema peripheral | | | |
| subjects affected / exposed | 26 / 464 (5.60%) | 31 / 453 (6.84%) | 54 / 277 (19.49%) |
| occurrences (all) | 26 | 32 | 91 |
| Fatigue | | | |
| subjects affected / exposed | 12 / 464 (2.59%) | 15 / 453 (3.31%) | 9 / 277 (3.25%) |
| occurrences (all) | 0 | 0 | 15 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 94 / 464 (20.26%) | 93 / 453 (20.53%) | 69 / 277 (24.91%) |
| occurrences (all) | 95 | 93 | 102 |
| Cough | | | |
| subjects affected / exposed | 62 / 464 (13.36%) | 75 / 453 (16.56%) | 44 / 277 (15.88%) |
| occurrences (all) | 63 | 75 | 56 |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 59 / 464 (12.72%) | 71 / 453 (15.67%) | 33 / 277 (11.91%) |
| occurrences (all) | 59 | 71 | 70 |
| Weight decreased | | | |
| subjects affected / exposed | 64 / 464 (13.79%) | 62 / 453 (13.69%) | 24 / 277 (8.66%) |
| occurrences (all) | 64 | 63 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 34 / 464 (7.33%) | 39 / 453 (8.61%) | 15 / 277 (5.42%) |
| occurrences (all) | 34 | 39 | 24 |
| Alanine aminotransferase increased | Additional description: AE not relevant to the trial | | |
| subjects affected / exposed | 15 / 464 (3.23%) | 39 / 453 (8.61%) | 35 / 277 (12.64%) |
| occurrences (all) | 15 | 39 | 80 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 21 / 464 (4.53%) | 26 / 453 (5.74%) | 38 / 277 (13.72%) |
| occurrences (all) | 21 | 26 | 85 |

| | | | |
|--|---------------------------|---------------------------|---------------------------|
| Blood creatine increased subjects affected / exposed occurrences (all) | 13 / 464 (2.80%) 0 | 14 / 453 (3.09%) 0 | 7 / 277 (2.53%) 7 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 18 / 464 (3.88%) 18 | 23 / 453 (5.08%) 23 | 13 / 277 (4.69%) 13 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 10 / 464 (2.16%) 0 | 7 / 453 (1.55%) 0 | 10 / 277 (3.61%) 13 |
| Paraesthesia subjects affected / exposed occurrences (all) | 25 / 464 (5.39%) 26 | 16 / 453 (3.53%) 16 | 17 / 277 (6.14%) 28 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 283 / 464 (60.99%) 284 | 293 / 453 (64.68%) 297 | 192 / 277 (69.31%) 409 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 184 / 464 (39.66%) 186 | 235 / 453 (51.88%) 237 | 122 / 277 (44.04%) 231 |
| Thrombocytopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 108 / 464 (23.28%) 109 | 222 / 453 (49.01%) 122 | 66 / 277 (23.83%) 111 |
| Leukopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 18 / 464 (3.88%) 18 | 29 / 453 (6.40%) 29 | 9 / 277 (3.25%) 15 |
| Lymphopenia alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 23 / 464 (4.96%) 23 | 23 / 453 (5.08%) 23 | 9 / 277 (3.25%) 22 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 25 / 464 (5.39%) 25 | 38 / 453 (8.39%) 38 | 7 / 277 (2.53%) 0 |

| | | | |
|--|--------------------|--------------------|-------------------|
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 21 / 464 (4.53%) | 2 / 453 (0.44%) | 34 / 277 (12.27%) |
| occurrences (all) | 0 | 0 | 62 |
| Conjunctivitis | | | |
| subjects affected / exposed | 13 / 464 (2.80%) | 1 / 453 (0.22%) | 27 / 277 (9.75%) |
| occurrences (all) | 0 | 0 | 63 |
| Eyelid oedema | | | |
| subjects affected / exposed | 2 / 464 (0.43%) | 2 / 453 (0.44%) | 9 / 277 (3.25%) |
| occurrences (all) | 0 | 0 | 9 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 220 / 464 (47.41%) | 246 / 453 (54.30%) | 85 / 277 (30.69%) |
| occurrences (all) | 221 | 250 | 134 |
| Vomiting | | | |
| subjects affected / exposed | 87 / 464 (18.75%) | 119 / 453 (26.27%) | 47 / 277 (16.97%) |
| occurrences (all) | 88 | 120 | 58 |
| Constipation | | | |
| subjects affected / exposed | 55 / 464 (11.85%) | 74 / 453 (16.34%) | 26 / 277 (9.39%) |
| occurrences (all) | 55 | 74 | 33 |
| Diarrhoea | | | |
| subjects affected / exposed | 48 / 464 (10.34%) | 64 / 453 (14.13%) | 26 / 277 (9.39%) |
| occurrences (all) | 49 | 64 | 27 |
| Stomatitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 35 / 464 (7.54%) | 14 / 453 (3.09%) | 13 / 277 (4.69%) |
| occurrences (all) | 35 | 14 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 25 / 464 (5.39%) | 15 / 453 (3.31%) | 16 / 277 (5.78%) |
| occurrences (all) | 25 | 15 | 24 |
| Abdominal pain | | | |
| subjects affected / exposed | 17 / 464 (3.66%) | 16 / 453 (3.53%) | 13 / 277 (4.69%) |
| occurrences (all) | 0 | 0 | 15 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|--|---------------------------|---------------------------|--------------------------|
| Alopecia subjects affected / exposed occurrences (all) | 17 / 464 (3.66%) 17 | 39 / 453 (8.61%) 39 | 9 / 277 (3.25%) 13 |
| Rash subjects affected / exposed occurrences (all) | 18 / 464 (3.88%) 0 | 13 / 453 (2.87%) 0 | 6 / 277 (2.17%) 8 |
| Pruritus subjects affected / exposed occurrences (all) | 5 / 464 (1.08%) 0 | 7 / 453 (1.55%) 0 | 7 / 277 (2.53%) 8 |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 68 / 464 (14.66%) 68 | 61 / 453 (13.47%) 61 | 69 / 277 (24.91%) 154 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 27 / 464 (5.82%) 27 | 29 / 453 (6.40%) 29 | 19 / 277 (6.86%) 27 |
| Arthralgia subjects affected / exposed occurrences (all) | 7 / 464 (1.51%) 8 | 23 / 453 (5.08%) 24 | 13 / 277 (4.69%) 20 |
| Bone pain subjects affected / exposed occurrences (all) | 13 / 464 (2.80%) 0 | 16 / 453 (3.53%) 0 | 7 / 277 (2.53%) 9 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 13 / 464 (2.80%) 0 | 14 / 453 (3.09%) 0 | 20 / 277 (7.22%) 25 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 101 / 464 (21.77%) 102 | 107 / 453 (23.62%) 109 | 50 / 277 (18.05%) 65 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 22 / 464 (4.74%) 30 | 24 / 453 (5.30%) 26 | 7 / 277 (2.53%) 0 |
| Hypoalbuminaemia | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 22 / 464 (4.74%) | 24 / 453 (5.30%) | 10 / 277 (3.61%) |
| occurrences (all) | 22 | 25 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 23 / 464 (4.96%) | 18 / 453 (3.97%) | 8 / 277 (2.89%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 17 / 464 (3.66%) | 16 / 453 (3.53%) | 4 / 277 (1.44%) |
| occurrences (all) | 0 | 0 | 9 |

| Non-serious adverse events | Pemetrexed maintenance population _Investigational arm | Gemcitabine maintenance population _Investigational arm | |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 112 / 115 (97.39%) | 139 / 142 (97.89%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 10 / 115 (8.70%) | 28 / 142 (19.72%) | |
| occurrences (all) | 3 | 13 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 58 / 115 (50.43%) | 66 / 142 (46.48%) | |
| occurrences (all) | 101 | 128 | |
| Pyrexia | | | |
| subjects affected / exposed | 9 / 115 (7.83%) | 23 / 142 (16.20%) | |
| occurrences (all) | 10 | 32 | |
| Chest pain | | | |
| subjects affected / exposed | 12 / 115 (10.43%) | 14 / 142 (9.86%) | |
| occurrences (all) | 18 | 21 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 21 / 115 (18.26%) | 19 / 142 (13.38%) | |
| occurrences (all) | 40 | 22 | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 115 (6.96%) | 12 / 142 (8.45%) | |
| occurrences (all) | 13 | 23 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--------------------------------------|--|-------------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 30 / 115 (26.09%) | 43 / 142 (30.28%) | |
| occurrences (all) | 42 | 79 | |
| Cough | | | |
| subjects affected / exposed | 21 / 115 (18.26%) | 32 / 142 (22.54%) | |
| occurrences (all) | 34 | 46 | |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 25 / 115 (21.74%) | 23 / 142 (16.20%) | |
| occurrences (all) | 41 | 40 | |
| Weight decreased | | | |
| subjects affected / exposed | 6 / 115 (5.22%) | 10 / 142 (7.04%) | |
| occurrences (all) | 0 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 12 / 115 (10.43%) | 11 / 142 (7.75%) | |
| occurrences (all) | 16 | 20 | |
| Alanine aminotransferase increased | Additional description: AE not relevant to the trial | | |
| subjects affected / exposed | 21 / 115 (18.26%) | 24 / 142 (16.90%) | |
| occurrences (all) | 33 | 38 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 27 / 115 (23.48%) | 21 / 142 (14.79%) | |
| occurrences (all) | 45 | 36 | |
| Blood creatine increased | | | |
| subjects affected / exposed | 4 / 115 (3.48%) | 8 / 142 (5.63%) | |
| occurrences (all) | 4 | 8 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 115 (1.74%) | 9 / 142 (6.34%) | |
| occurrences (all) | 3 | 11 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 5 / 115 (4.35%) | 8 / 142 (5.63%) | |
| occurrences (all) | 8 | 11 | |
| Paraesthesia | | | |
| subjects affected / exposed | 11 / 115 (9.57%) | 23 / 142 (16.20%) | |
| occurrences (all) | 16 | 42 | |

| | | | |
|--|-------------------|--------------------|--|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 80 / 115 (69.57%) | 112 / 142 (78.87%) | |
| occurrences (all) | 192 | 236 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 51 / 115 (44.35%) | 62 / 142 (43.66%) | |
| occurrences (all) | 122 | 104 | |
| Thrombocytopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 33 / 115 (28.70%) | 59 / 142 (41.55%) | |
| occurrences (all) | 59 | 108 | |
| Leukopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 115 (4.35%) | 11 / 142 (7.75%) | |
| occurrences (all) | 9 | 16 | |
| Lymphopenia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 115 (4.35%) | 11 / 142 (7.75%) | |
| occurrences (all) | 7 | 10 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | 5 / 142 (3.52%) | |
| occurrences (all) | 0 | 0 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 14 / 115 (12.17%) | 1 / 142 (0.70%) | |
| occurrences (all) | 23 | 1 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 18 / 115 (15.65%) | 2 / 142 (1.41%) | |
| occurrences (all) | 38 | 2 | |
| Eyelid oedema | | | |
| subjects affected / exposed | 6 / 115 (5.22%) | 0 / 142 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| alternative assessment type: Systematic | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 38 / 115 (33.04%) | 47 / 142 (33.10%) | |
| occurrences (all) | 54 | 72 | |
| Vomiting | | | |
| subjects affected / exposed | 19 / 115 (16.52%) | 21 / 142 (14.79%) | |
| occurrences (all) | 21 | 29 | |
| Constipation | | | |
| subjects affected / exposed | 14 / 115 (12.17%) | 12 / 142 (8.45%) | |
| occurrences (all) | 15 | 18 | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 115 (12.17%) | 12 / 142 (8.45%) | |
| occurrences (all) | 16 | 17 | |
| Stomatitis | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 4 / 115 (3.48%) | 0 / 142 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 115 (4.35%) | 11 / 142 (7.75%) | |
| occurrences (all) | 7 | 14 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | 7 / 142 (4.93%) | |
| occurrences (all) | 3 | 10 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 6 / 115 (5.22%) | 17 / 142 (11.97%) | |
| occurrences (all) | 9 | 23 | |
| Rash | | | |
| subjects affected / exposed | 7 / 115 (6.09%) | 4 / 142 (2.82%) | |
| occurrences (all) | 8 | 4 | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 115 (5.22%) | 2 / 142 (1.41%) | |
| occurrences (all) | 6 | 2 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 29 / 115 (25.22%) | 26 / 142 (18.31%) | |
| occurrences (all) | 52 | 64 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| Back pain subjects affected / exposed occurrences (all) | 7 / 115 (6.09%) 11 | 19 / 142 (13.38%) 29 | |
| Arthralgia subjects affected / exposed occurrences (all) | 12 / 115 (10.43%) 18 | 9 / 142 (6.34%) 16 | |
| Bone pain subjects affected / exposed occurrences (all) | 6 / 115 (5.22%) 10 | 7 / 142 (4.93%) 10 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 7 / 115 (6.09%) 9 | 9 / 142 (6.34%) 9 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 19 / 115 (16.52%) 25 | 13 / 142 (9.15%) 20 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 1 / 115 (0.87%) 0 | 2 / 142 (1.41%) 0 | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 4 / 115 (3.48%) 0 | 6 / 142 (4.23%) 0 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 3 / 115 (2.61%) 0 | 6 / 142 (4.23%) 0 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 6 / 115 (5.22%) 9 | 4 / 142 (2.82%) 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 23 August 2012 | This 1st substantial modification aims to add investigator centres, to delete the centre of Saint-Brieuc, to modify the rhythm of the evaluations and to clarify the protocol (minor corrections). |
| 07 November 2012 | This 2nd substantial amendment aims to : <ul style="list-style-type: none">- Add investigator centres- Change the address of one centre (Toulon CHI)- Decrease the delay between bone radiotherapy and gemcitabine chemotherapy in accordance with the MA.- Clarify the criteria for non-inclusion of brain metastases and superior vena cava syndromes- Correct consent following review by a patient committee |
| 24 September 2013 | This 3rd substantial amendment aims to : <ul style="list-style-type: none">- Add and remove investigating centres- Adding details to the protocol: delay in the start of treatment, dose adaptations and dose caps. |
| 24 March 2014 | This 4th substantial amendment aims to : <ul style="list-style-type: none">- Add and delete investigating centres- Clarify the protocol: timeline to the start of treatment, dose adaptations and dose caps. |
| 01 December 2015 | This 5th substantial amendment aims to : <ul style="list-style-type: none">- Change the principal investigators of 6 centres.- Clarify the management of toxicities. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35051725>